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1. Pharmacology of Drugs of Abuse

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Introduction: Drug taking is increasing dramatically, particularly among young people. One reason for this is that illicit drugs affect brain chemistry to produce a pleasurable experience. With almost all substances, this is due to the effect of dopamine in the nucleus accumbens. In addition, their individual chemical structures determine their toxicodynamics and toxicokinetics, leading to a wide range of wanted and unwanted effects, and. Those involved in clinical toxicology and emergency medicine therefore need to have a basic understanding of the ways in which the different illicit drugs produce their effects. Some examples are given in this abstract, more will be presented. *Heroin:* Heroin crosses the blood-brain barrier very rapidly, which is why it is the most widely abused opioid. It then breaks down almost immediately to monoacetylmorphine and morphine, which combine with opioid receptors to produce the wanted and unwanted effects. One of the remarkable pharmacological properties of opioids, particularly heroin, is tolerance. Tolerance to heroin is very marked: the initial dose to produce an effect is a few milligrams, and ten milligrams of pure heroin could be fatal by intravenous injection in a drug-naïve individual. However, the average user who seeks help is taking about 750 milligrams of street heroin a day. Overdose can occur from three main causes. The initial dose may be too much, the supply may be of greater purity than usual (though this should not be a problem for the tolerant user), and tolerance may be lost after a few days' abstinence. When this happens, the dose which was taken regularly just a few days beforehand, now becomes potentially lethal. Naloxone acts as an antagonist at opioid receptors, reversing the toxic effects of opioids. Methadone replacement therapy given daily, orally or by injection is used as a way of managing heroin addiction, and has widespread support as it reduces injecting behaviour and criminal activity. However it involves long term use of another opioid, and so is in effect replacing one addiction with another. *Cocaine:* The effects of cocaine are mainly due to two related pharmacological properties. The first is that it blocks the reuptake of dopamine, which causes the euphoric ''high'' but which may also lead to confusion, aggression, hallucinations and possibly convulsions. Reuptake of serotonin is also inhibited. The second main property is that it blocks the reuptake of noradrenaline, which causes marked vascular effects, causing a very high blood pressure and possibly chest pain, which is the commonest reason for cocaine users to seek medical advice. Large amounts can also cause hypotension due to sodium channel blockade. Cocaethylene is the ethyl metabolite of cocaine, produced in the liver when alcohol is present. There is no antidote for cocaine toxicity; the main medical treatments include oxygen, diazepam to reduce central and peripheral nervous system activity and lower blood pressure, nitrates to relieve coronary spasm and further control blood pressure, and aspirin for the patient with chest pain. *Amphetamine and Methamphetamine:* These drugs and related compounds have marked stimulant and sympathomimetic effects, related to their similarity to catecholamines. Euphoria, central nervous system stimulation, appetite suppression, energy, tachycardia and other symptoms occur. *Ecstasy:* This drug 3,4-methylenedioxymethamphetamine (MDMA: ecstasy) is related to amphetamine. It has acquired a reputation as a dance drug, because of its unique pharmacological effects, which can be summarised as ''euphoria, empathy and energy.'' It causes the release of large amounts of serotonin in the central nervous system, followed by depletion, and possibly neurotoxicity. Dopamine is also released. It causes secretion of antidiuretic hormone, so that any excess water consumed is not eliminated. *Cannabis:* Tetrahydrocannabinol, the active ingredient combines with receptors in the brain and periphery to cause mental effects together with vasodilatation and tachycardia. Effects last a few hours, but the drug can persist in tissues for a long time. Acute overdose is unlikely to be fatal, but heavy use appears to be cumulative and can lead to agitation, hallucinations and paranoid behaviour. *Conclusion:* It will be seem from these examples that there is a need to understand the link between the pharmacology of illicit drugs and their potential clinical effects. This can lead to more rational management of toxicity.

2. Management of Toxicity from Cocaine and Other Sympathomimetics

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Sympathomimetics may be defined as agents that either directly or indirectly interact with alpha- and beta-adrenergic receptors. Although prototypical agents such as cocaine or amphetamines have relatively balanced effects at these receptors, certain sympathomimetic agents may preferentially stimulate either receptor subtype; phenylpropanolamine, which is predominately alpha-adrenergic or clenbuterol, which is predominately beta-adrenergic. Loosely speaking, drug or food interactions with monoamine oxidase inhibitors may also be classified as fundamentally sympathomimetic. However, the discussion will focus on sympathomimetic drugs of abuse. A thorough knowledge of the functions of each receptor subtype (i.e. $alpha_1$, $alpha_2$, $beta_1$, $beta_2$, $beta_3$) not only helps to understand many of the specific adverse effects associated with these agents, but also provides insight into appropriate therapy. Predictable toxic events result from; hypertension and vasospasm mediated by alpha-adrenergic agonism, tachycardia largely mediated by beta-adrenergic agonism, and increased sheer force (dp/dt) on vessels mediated by the combined effects of hypertension and tachycardia. These mechanisms produce ischemia to virtually any organ system, or, alternatively can result in hemorrhage from vessel rupture. Additionally, certain sympathomimetic agents produce toxic effects that relate to other mechanisms of action. For example, cocaine blocks fast sodium channels in cardiac conduction tissue, prevents the reuptake of serotonin and other biogenic amines, stimulates the release of excitatory amino acids, and is prothrombotic as a result of accelerated atherogenesis, enhanced platelet aggregation and impaired thrombolysis (increases TPA-inactivator). Amphetamines also block the reuptake of biogenic amines and enhance excitatory amino acids, but unlike cocaine, they have weak inhibitory effects on monoamine oxidase. Additional predictable toxicities from these effects include psychomotor agitation, seizures and hyperthermia, with attendant rhabdomyolysis and the potential for multiorgan failure. Although hypertension and tachycardia are often the most overt manifestations of clinical toxicity, animal models and human experience clearly demonstrate that the most immediate life-threatening event is hyperthermia (1,2). Critical elevations in temperature should be treated with rapid cooling, volume resuscitation and sedation. While advocated by some, evidence to support the use of dantrolene is lacking. Hypertension and tachycardia usually responds to sedation, indicating either a primary role for agitation in the genesis of these abnormalities, or peripheral effects of benzodiazepines on cardiovascular receptors. The use of beta-adrenergic antagonists and mixed alpha- and beta-adrenergic antagonists are absolutely contraindicated when alpha-adrenergic effects are present. Vasospasm can be treated with phentolamine or a direct acting vasodilator such as nitroglycerin or nitroprusside. Cardiovascular complications generally respond to most standard therapies. An exception can be made for the treatment of wide-complex dysrhythmia in the setting of cocaine toxicity. Here, as with other sodium channel blockers, the use of hypertonic sodium bicarbonate is preferred over antidysrhythmic agents. Recent lines of investigation include toxin directed antibodies and exogenous enzymes. Although not yet available for clinical use, these potential new therapies will be discussed in detail (3,4). *References:* 1. Catravas JD, Waters IW. Acute cocaine intoxication in the conscious dog: Studies on the mechanism of lethality. *J Pharmacol Exp Ther* 1981; 217:350–356. 2. Marzuk PM, Tardiff K, Leon AC, et al. Ambient temperature and mortality from unintentional cocaine overdose. *JAMA* 1998; 279:1795–1800. 3. Sun H, Shen ML, Pang YP, Lockridge O, Brimijoin S. Cocaine metabolism accelerated by a re-engineered human butyrylcholinesterase. *J Pharmacol Exp Ther* 2002; 302:710–716. 4. Duysen EG, Bartels CF, Lockridge O. Wild-type and A328W mutant human butyrylcholinesterase tetramers expressed in Chinese hamster ovary cells have a 16-hour half-life in the circulation and protect mice from cocaine toxicity. *J Pharmacol Exp Ther* 2002; 302:751–758.

3. Drug Facilitated Sexual Assault—Epidemic or Urban Myth?

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Introduction: Drug facilitated sexual assault (DFSA) is the administration of a substance to a victim for the purpose of facilitating nonconsensual sexual relations such as rape. The substance, often a drug, is administered surreptitiously or knowingly to the victim. The intent is to impair the victim's ability to resist and remember the sexual assault. The most common mode is adulteration of a beverage. ''Drink spiking'' is a similar phenomena but the intent is not always sexual assault but robbery, humiliation or other intentions. An ideal DFSA agent would induce anterograde amnesia, disinhibition and immobilization; be uncommon and unexpected; relatively tasteless, odorless and not visibly detectable in a beverage; difficult for the toxicology laboratory to detect with a narrow window of laboratory detection; and have a high potency, rapid onset and

brief duration of effect. Many DFSA agents are not ideal and are readily detected through lingering clinical effects on the victim or by a forensic toxicology laboratory. A committee of the Society of Forensic Toxicologists recently published a list of over 50 substances believed to have been used in DFSA. This list of 50 substances includes gamma-hydroxybutyrate (GHB) and analogs, ethanol, sedatives, muscle relaxers, marijuana (THC), stimulants, dissociative agents, anticholinergics, antipsychotics, antidepressants, opiates and clonidine (1). A few of these agents are close to ideal; specifically GHB and several high potency, short acting, uncommon benzodiazepines. Sufficient doses of GHB may cause a rapid onset, but short duration of deep sedation associated with amnesia, disinhibition and physical immobilization. The reported plasma elimination half life varies from 27 to 53 min. The length of time that GHB may be detected in the blood is less than 8 h and in the urine is no more than 8 to 12 h after dosing. *Prevalence:* The prevalence of illicit acts such as rape, DFSA and drink spiking are difficult to measure. An estimated 300,000 sexual assaults occur annually in the USA, with only 90,000 cases reported (2). DFSA represents a substantial proportion of reported sexual assault varying from 12% to 21% (3,4). In response to a 1999 Glamour Magazine survey, 19% of 200 young women reported that they knew someone who was a victim of DFSA with GHB (5). DFSA victims may be reluctant to report these crimes to police for a variety of reasons, i.e. they may suffer from partial or complete amnesia, the perpetrator may be a friend or coworker or they may feel complicit because they were drinking ethanol and or using illicit drugs. While data from police, rape counselling services and surveys indicate an increasing prevalence of DFSA, until recently there have been little objective data from laboratory studies to evaluate these claims. Most of the early evidence came from prosecution of perpetrators. Some perpetrators recorded their crimes on video tapes, which were later confiscated along with supplies of DFSA agents. However, arrest and convictions of DFSA perpetrator are relatively rare. One reason for a low arrest and conviction rate was the lack of supportive laboratory evidence. *Toxicology Laboratory Testing:* When DFSA recently became a growing concern in the US in the early 1990's, perpetrators could choose from a larger variety of DFSA agents which were not detected by standard emergency department or even forensic toxicology laboratory testing. In the late 1980's and early 1990's, most of these laboratories did not routine perform procedures that could detect GHB and some benzodiazepines like flunitrazepam. However, in the early 1990's, most US forensic toxicology laboratories began to modify their benzodiazepine screens to include enzyme hydrolysis and lowered their threshold levels resulting in dramatically improved benzodiazepine screening sensitivity. Even with more rigorous analytic methods, positive drug screens except for ethanol in suspected DFSA cases were uncommon. One possible explanation was that DFSA victims were presenting too late for examination and beyond the window of detection for high potency, rapidly eliminated DFSA agents. With support from Roche Pharmaceutics, manufacturer of the alleged ''Date Rape'' drug flunitrazepam (Rohypnol), ElSohly offered free laboratory analysis for suspected DFSA cases culminating in the largest published series of analytical laboratory results (6). Of their 3303 samples analyzed, ethanol was detected in 41%, THC 19%, benzodiazepines (excluding flunitrazepam) 9%, cocaine 8%, amphetamines 6%, GHB 3%, opiates 3%, propoxyphene 1%, barbiturates 1%, and flunitrazepam 0.3%. Samples were collected in less than 24 h after the alleged incident in 73% of these cases but the proportion collected in less than the critical 12 h period was not reported. GHB and some high potency, short acting benzodiazepines cannot be detected in the urine beyond 12 from ingestion. Several other reports with much smaller sample sizes had similar findings until 2003. In July 2003, Hansson reported on the results of analysis of 48 cases of DFSA in Western Australia (7). Ethanol was detected in 80% of his cases with 46% having a concentration in blood or urine greater than 0.15%. Other drugs detected in Hansson's cases included methylamphetamine (3), amphetamine (1), methylenedioxymethamphetamine (MDMA) (1), THC (1), benzodiazepines (0), GHB (0) and ketamine (0). Similar findings were reported by the New Zealand Institute of Environmental Science and Research on 162 DFSA samples (8). None had shown any trace of known date-rape drugs, such as GHB or ketamine but high levels of alcohol were found in a large number of samples. Six samples tested positive for sedatives in patients not previously taking the drugs. The relatively large proportions of high levels of ETOH in suspected victims of DFSA or drink spiking has only been shown in New Zealand and Australia. Other areas of the world should measure quantitative ETOH levels in current or future DFSA lab studies. Urine ETOH levels have an excellent correlation with concurrently drawn blood ETOH levels. Whether urine ETOH levels, collected hours after one has stopped ingesting ETOH, can give some indication of how high the blood ETOH level had been is yet to be determined. The ability of hair shaft and bulb analysis to detect DFSA agents after a single dose has been demonstrated experimentally and to a very limited extent in DFSA cases. Hair analysis has been used to demonstrate evidence after single doses of GHB, flunitrazepam, bromazepam, lorazepam, pentobarbital, zolpidem and MDMA. The potential for hair analysis to detect rapidly eliminated DFSA agents in a victim who presents late is very exciting. *Conclusions:* Early toxicology laboratory studies of suspected DFSA victims showed that ETOH was the most common intoxicating substance detected. Recent studies in Australia and New Zealand suggest that a large proportion of suspected victims of DFSA and drink spiking have surprising high levels of ETOH. Whether this is a universal finding and whether these victims or their partners are primarily responsible for the high ETOH levels are yet to be determined. The failure to detect GHB and other short duration DFSA agents in these victims may be a result of collecting specimen too late or because they were never there in the first place. Recent advances in the analysis of blood, urine and hair specimen will help to

enhance our understanding of DFSA. *References:* 1. Juhascik M, Le NL, Tomlinson K, Moore C, Gaensslen RE, Negrusz A. Development of an analytical approach to the specimens collected from victims of sexual assault. *J Anal Toxicol* 2004; 28(6):400–406. 2. Negrusz A, Goldstein PJ, Levy PS. Estimate of the incidence of drug-facilitated sexual assault in the United States. Proceedings of the 39th Annual The International Association of Forensic Toxicologists (TIAFT) Meeting, August 2001, Prague, Czech Republic. 3. McGregor MJ, Lipowska M, Shah S, et al. An exploratory analysis of suspected drug-facilitated sexual assault seen in a hospital emergency department. *Women Health* 2003; 37(3):71–80. 4. Moreton R, Bedford K. Spiked drinks: A focus group study of young women's perceptions of risk and behaviours. Central Sydney Area Health Service, Available at: www.cs.nsw.gov.au/pophealth/dph/women/projects. 5. Nordenberg T. Raising consciousness about drugs and rape. FDA Consumer Mar 1, 2000. 6. Hindmarch I, ElSohly M, Gambles J, et al. Forensic urinalysis of drug use in cases of alleged sexual assault. *J Clin Forensic Med* 2001; 8:197–205. 7. Hansson R. Western Australia Chemistry Centre Annual Review 2002–03; presented July 17th, 2003 at the Australasian Drug Strategy Conference in Alice Springs, Australia. 8. Date-rape druggings rare, scientists find. New Zealand Herald September 1, 2003.

4. Problems of Managing Drug Mules

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Introduction: Mules or body packers or body baggers that may also called ''swallowers'' or ''internal carriers'' are persons who smuggle illicit drugs. The term ''body stuffing'' inappropriately used synonymously with body packing, refers to the swallowing of relatively small amounts of loosely wrapped drug because of the fear of arrest (1). Body packers may smuggle cocaine, heroin, opium, hashish, marijuana, amphetamines, 3,4 methylenedioxymethamphetamine or any other illicit drug. Occasionally they ingest more than one type of drug. Drugs are mostly swallowed as small packages usually wrapped in cellophane, layers of latex, robber cots, condoms, plastic bags, aluminum foil, plastic foil, wax sealing, carbon paper or self adhesive tape. The first report of mules was from Toronto in 1973 about a patient who had swallowed a condom filled with hashish. He developed small-bowel obstruction 13 days after, but survived following surgery (2). The transportation of illicit drugs by internal concealment has since evolved in many countries. In 1993–94, 30 persons arrested in Frankfurt airport for smuggling internally concealed cocaine. They all had positive x-ray and the amount of cocaine hydrochloride found in particular cases ranged from 242 to 1050 g net weight, divided into containers weighing from 5.7 to 13.8 g. The number of concealed containers ranged from 44 to 135 per person (3). A review of 50 body packer deaths in New York City from 1990 to 2000 revealed that 42 were transporting opiates, 4 cocaine and 4 both opiates and cocaine (4). *Diagnosis:* A detailed history including information about the drug packets (the type of drug, the nature of wrapping and the number of packets) and gastrointestinal symptoms (vomiting, pain, obstipation and constipation) should be obtained. Body packers generally know the number of packets they carry, in order to determine when passage is complete. However, they are often dishonest historians. Physical examination may help identify drug-induced toxic effects in a body packer, if a package leaks or ruptures. Opium or heroin overdose causes sedation, miosis and diminished bowel sounds, which generally precede the onset of lethal respiratory depression. Cocaine overdose causes anxiety, dilated pupils, diaphoresis, tachycardia and hypertension followed by hyperthermia, seizures and cardiovascular collapse. The abdominal examination may reveal distention or palpable packets. Gentle rectal and vaginal examinations may also disclose packets. Several large studies revealed that plain abdominal x-ray has a sensitivity of 76 to 90% (5–7). However, false positive due to bladder stones, inspissated stool or intra-abdominal calcifications and false negative x-ray due to low density of the drug, wrapping material (cellophane), low technical quality and the reader's inexperience may occur. Contrast mediated abdominal radiography identify drug packets as filling defects within the contrast media. Both false positive and false negative were only 4%. However, CT scan provides more accurate picture and higher sensitivity. In my experience on 56 cases with opium and heroin body packers, sensitivity of CT scan was 100% and will be presented in details. Ultrasound does not have the same sensitivity to detect foreign bodies in the small or large bowel. Magnetic Resonance Imaging does not have any diagnostic value of drug packets in the bowel (8). Toxicological analyses of the urine or blood is only confirmatory in the symptomatic patients. Body packing may cause unexpected sudden death. Four such cases were reported from Hamburg, Germany (9). Severe intoxication, bowel obstruction, gastric retention and even esophageal obstruction are the main complications. *Management:* Unless the patient is being prepared for immediate surgery, gastrointestinal decontamination should be attempted. Activated charcoal reduces the lethality of cocaine and should be administered 1 g/Kg (up to 50 g) orally every 4 hours with a laxative (sorbitol 100 mg/Kg). The efficacy of naloxone in opium and heroin body packers limits the importance of activated charcoal. Whole–bowel irrigation with a polyethylene glycol-electrolyte lavage solution (2 L/hr in adults) results in a relatively gentle evacuation of the gastrointestinal tract and is safe for use in body packers. The use of oil

based laxatives, although recommended in the past, should be avoided because they reduce the tensile strength and burst the latex wrapped packets. Endoscopies are only indicated in a patient who only one packet fails to pass the pylorus. Surgery is required for patients with esophageal or gastrointestinal obstruction or perforation and in severe intoxication which does not respond to medical treatment. Following surgical emptying of the gastrointestinal tract, a final CT scan should be performed to document the clearance of packets. This should also be undertaken after medical treatment and three packet free stools (1). *Conclusion:* The care of body packers is challenging and may tax the most competent physician. It is thus recommended to observe these patients very carefully and to manage them appropriately. Involvement of hospital-based legal counsel and the patient's ethics committee are suggested to avoid any legal and ethical disruption. *References:* 1. Traub SJ, Hoffman RS, Nelson LS. Body packing-The internal concealment of illicit drugs. *N Eng J Med* 2003; 349:2519–2526. 2. Deitel M, Syed AK. Intestinal obstruction by an unusual foreign body. *Can Med Assoc J* 1973; 109:211–212. 3. Bogusz MJ, Althoff H, Erkens M, et al. Internally concealed cocaine: Analytical and diagnostic aspects. *J Forensic Sci* 1995; 40:811–815. 4. Gill JR, Graham SM. Ten years of body packers in New York City: 50 deaths. *J Forensic Sci* 2002; 47:843–846. 5. McCarron MM, Wood JD. The cocaine body packer syndrome: Diagnosis and treatment. *JAMA* 1983; 250:1417–1420. 6. Utecht MJ, Stone AF, McCarron MM. Heroin body packers. *J Emerg Med* 1993; 11:33–40. 7. Afshar M, Hosniam H, Aboul-Massoomi Z, et al. The study of suspicious cases of body smuggling in Laghman hospital 1999–2000. *Arch Iranian Med* 2002; 5:205–206. 8. Hergan K, Kofler K, Oser W. Drug smuggling by body packing: What radiologists should know about it. *Eur Radiol* 2004; 14:736–742. 9. Heinemann A, Miyaish S, Iwersen S, et al. Body packing as cause of unexpected sudden death. *Forensic Sci Int* 1998; 92:1–10.

5. Drug Abuse and Pregnancy

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Objective: Drug abuse during pregnancy is one of the most difficult and emotive of all drug safety issues that raises concerns regarding both maternal and fetal well-being. It often presents parents and clinicians with ethical, medico-legal and emotional dilemmas as to whether the pregnancy should continue (1). Although the methods of collecting and analysing such data are highly variable, it is apparent that the number of people with illicit drug problems has increased over the past 5 years (2–5). In the UK, based on a population aged 16–74 years is estimated that drug abuse is more common in men than in women (32% vs 21%), but it is generally recognised that the statistics for women are under-reported (2,6). Among women dependency patterns vary with age and ethnicity (2). 17% of drug users reported injecting their drugs, the mean age being 21 y. The starting age range was 11–44 years with 9% being under 16 years (1). Cannabis (24%) is the most commonly self-reported drug followed by amphetamines (7%). The lifetime prevalence rates for cocaine, ecstasy and LSD were approximately 4% compared with 3% for tranquillisers and 1% for volatile substances. There is equivocal data on the use of anabolic steroids and misuse of prescription medicines by women (3–5). The effects of alcohol, tobacco and caffeine are excluded from this paper. *Methods:* Most of the studies of drug abuse in pregnancy have serious limitations; the choice of a suitable control group is difficult (drug users vs. non-drug users) and there are numerous potential confounders. For example, multiple drug use (including alcohol or smoking, caffeine), the dose and purity of the substance, infections (STD, HIV), ill-defined nutritional status, insufficient antenatal care, obstetric and neonatal risk factors and excessive dropouts, must be addressed, but are difficult to control and evaluate. There is growing concern about the long-term effects on postnatal development, for which currently there are no prenatal diagnostic tests. *Results:* Evaluation of dose response relationships is difficult and as illicit drugs can cause fetotoxicity at any stage of pregnancy establishing a causal relationship is not often possible. Little is known about the fetotoxicity of substances such as GHB, ketamine, psilocybine, phencyclidine and solvents unless accompanied by severe maternal toxicity. Although there are isolated reports of miscarriages, CNS, eye, and limbs malformations in infants born to women taking LSD, no causal relationship has been established. There is no clear evidence that the misuse of benzodiazepines is associated with an increased risk of malformations. Chronic use, especially near term has been associated with the 'floppy infant' syndrome. Changes in legislation concerning the use of cannabis may over time increase our knowledge of its reproductive effects. There are isolated case reports of malformations following cannabis (smoking or inhalation) use in pregnancy, but no conclusive evidence to indicate an increased incidence of malformations. Cannabis use is strongly associated with the use of tobacco and alcohol, which can be fetotoxic also. Cumulative data on heroin and methadone misuse provide no convincing evidence of an increased risk of malformations, but there is evidence of increased neonatal toxicity and SIDS. The limited data on buprenorphine use in the management of opiate dependence is encouraging (7). Cocaine, crack and derivatives have been clearly associated with an increased incidence of abruptio placentae, maternal and neonatal intracranial haemorrhage. However, the alleged association

with urogenital defects and gastroschisis remains unproven. Amphetamines and related stimulants have been associated with an increased risk of CVS malformations in animals, but evidence is lacking in human pregnancy (5). Chronic use of amphetamines has been associated with an increased risk of miscarriage. The illicit use of ecstasy (methylenedioxymethamphetamine, MDMA) has increased over the past decade and there is growing concern about its potential neurotoxicity. The age group of users means that exposure in early pregnancy is likely but few data exist on fetotoxicity (6,8,9). NTIS has collected prospective follow up data on the outcome of 201 ecstasy exposed pregnancies in the UK. The data indicate that ecstasy may be associated with a two–fold increased risk of malformations. CNS, cardiovascular and musculoskeletal anomalies were predominant (9). In general, prematurity, meconium stained fluids, IUGR, reduced birth weight and head circumference and neonatal death are common in infants born to drug misusers. There are conflicting reports on whether there is a higher risk of SIDS possibly related to abnormal sleep patterns and impaired hypoxia arousal. A high proportion of babies have neonatal withdrawal symptoms (tremor, hypertonicity, irritability, diarrhoea, vomiting, abnormal sleep patterns and altered visual responses) which may last up to several weeks occur. Data are limited and inconsistent on the possible adverse effects of illicit drugs on postnatal development. *Conclusion:* Maternal exposure to drugs of abuse has been associated with fetal and neonatal toxicity, but not specifically with congenital malformations. In most cases it is not clear whether the toxicity is drug related or due to deficits in socio-economic lifestyle. Evidence concerning fetotoxicity from paternal exposure is lacking. Drug-dependent mothers and their babies, 'the hidden users' represent a unique group that requires further investigation, especially as regards long-term postnatal development. *References:* 1. McElhatton P. The effects of drug misuse in pregnancy. In: Children exposed to substance misuse—Implications for family placement. Ed. Rena Philips. BAAF publication 2004, pp. 43–72. 2. ONS Report: Tobacco, alcohol and drug use and mental health. HMSO (2002). 3. Home office on-line report 33/03. 2003. 4. National Institute of Drug Abuse (NIDA). Info facts. US Department of Health. March 2004. 5. DrugScope. FAQs http://www.drugscope.org.uk/druginfo/drugsearch December 2004. 6. Bateman DN, McElhatton PR, Dickinson D, et al. A case control study to examine the pharmacological factors underlying ventricular septal defects in the North of England. *EJCP* 2004; 60(9):635–641. 7. Turning Point, Alcohol and Drugs Centre. Victoria, Australia. December 2003. 8. McElhatton PR, Bateman DN, Evans C, KR Pughe, Thomas SHL. Congenital anomalies after pre-natal ecstasy exposure. *Lancet* 1999; 354:1441–1442. 9. McElhatton P, Hedgley C, Thomas S. Congenital anomalies after prenatal ecstasy exposure. BJCP 2005. In press.

6. Opioids-Current Issues

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Clinical application of the recent research in opiate neuropharmacology will change the treatment of opiate dependence and withdrawal. The opioid system consists of three G protein-coupled receptors, mu, delta, and kappa, which are stimulated by a family of endogenous opioid peptides. They can also be activated exogenously by alkaloid opiates. Activation of μ-opiate receptor results in calcium influx through the NMDA receptor ion-channel complex which activates various calcium dependent second messenger systems. Mu receptors are in all areas of brain belonging in the circuits of addiction and are of primary importance for mediating analgesic and addictive effects. Addictive properties are abolished in mice lacking μ opiate receptor. Drugs that affect these receptors are central in development of addiction therapies. Genetic influences affect μ receptors. The clinical relevance of research on the multiple μ receptors is discussed. There is evidence that NMDA receptor antagonist treatment can prevent development of opiate dependence. Glutamate is the major excitatory neurotransmitter in the CNS. Glutamate receptors have been divided into NMDA and non-NMDA receptors based on their pharmacologic and physiological properties. Blocking NMDA receptors can prevent withdrawal in morphine dependent adult animals, but not neonatal rats. In the young, different factors may activate second messenger systems. Causes of physical dependence and drug seeking behavior include physical changes in neurons as well as dysregulation of the hypothalamic-pituitary-adrenal response to stress. Chronic morphine selectively sensitizes norepinephrine sensitive neurons in the locus cereleus. Hyperresponsiveness of this system is manifest by hyperarousal, attentional dysfunction, and anxiety, and sleep disturbances. Drug seeking behavior occurs in an effort to counteract the hypersensitivity of this system. It is difficult to map the reward system. Enhancement of dopamine secretion in the nucleus accumbens, mu opiate receptors in the locus cereleus which mediate inhibitory action of opiates on noradrenergic nuerons, and glutamergic pathways play a role in neuroplastic changes that occur with opiate abuse. Activation of mu receptors may result in a broad recruitment of neurotransmitter systems that cause addictive behavior. Other applications of recent neuropharmacology opiate research are discussed. A short history of opiate use/abuse is reviewed as well as some popular methods of abuse (such as ''Chasing the Dragon''). *References:* Noda Y, Nabeshima, Opiate physical dependence and NMDA receptors. *Eur J Pharm* 2004; 500:121–128. Pasternak G. Multiple opiate receptors: déjà vu all over again. *Neuropharmacology*

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7. Pharmacotherapy of Ethanol Abuse

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Although ethanol has been used and abused by mankind for millennia and is among the most intensively studied drugs, relatively little is known about its effects on the human brain. Ethanol has many defined pharmacological effects, including altering protein structure by binding to their hydrophobic pockets and interactions with an array of receptors and ion channels, though there is no unifying understanding of its mechanism of action. For this reason little drug specific pharmacotherapy has evolved to prevent or treat ethanol abuse. Until recently only two medications, disulfiram and naltrexone, had been widely accepted for the treatment of alcohol dependence. Disulfiram, an aldehyde dehydrogenase inhibitor, works through negative reinforcement by producing flushing, headache and vomiting following the conversion of ingested ethanol to acetaldehyde. Other forms of aversive therapy include the use of dangerous emetics, such as antimony, to ethanol to reduce consumption (1). Success is low with disulfiram and other aversives unless the drug's administration is strictly supervised. Naltrexone, an opioid antagonist, interferes with the expected positive reinforcement provided by ethanol and mediated by dopamine release in the nucleus accumbens. Naltrexone may have a greater benefit in a selected group of patients with a genetic polymorphism of the opioid receptor (2). Stimulation of the N-methyl-D-aspartate (NMDA) receptor in the ventral tegmental area also induces dopamine release in the nucleus accumbens. Acamprosate, used for decades in Europe and recently approved in the US for the treatment of alcoholism, blocks primarily the stimulation by glutamate of the NMDA receptor (3). Efficacy of acamprosate is moderate but relatively consistent among studies. Although the causal effects of low central nervous system serotonin levels are unclear, there is an association with altered dopaminergic function. Selective serotonin reuptake inhibitors (SSRI's) have shown limited efficacy in ethanol dependence, and an enhanced response in genetically unique populations has been implicated. Given the complexity of the serotoninergic neurotransmitter system it has been difficult to determine which if any receptor subtypes are specifically involved and which pharmacotherapies (paroxetine, sertraline, buspirone, lithium) are most effective. Given the importance of dopamine in the ''final common pathway'' neurobiology of ethanol and other drugs of abuse, pharmacotherapy has focused on reducing dopamine receptor activity in the mesolimbic. Haloperidol and several atypical antipsychotics have been demonstrated effective, although variably so. Aripiprazole, a dopamine-2 receptor partial agonist, has theoretical benefit but no supporting evidence for efficacy at the current time. Given both the lack of a fundamental understanding of the mechanism and the lack of adequate documentation of safety and efficacy of the current regimens it follows that physicians are generally unwilling to prescribe pharmacotherapy for patients with alcohol abuse (4). Fortunately, the increasing insight into the pharmacogenetics of alcohol abuse holds promise that a better understanding of its underpinnings will become available in the near future (5). *References:* 1. Tarabar AF, Khan Y, Nelson LS, Hoffman RS. Antimony toxicity from the use of tartar emetic for the treatment of alcohol abuse. *Vet Hum Toxicol* 2004; 46(6):331–333. 2. Oslin DW, Berrettini W, Kranzler HR, Pettinati H, Gelernter J, Volpicelli JR, O'Brien CP. A functional polymorphism of the mu-opioid receptor gene is associated with naltrexone response in alcohol-dependent patients. *Neuropsychopharmacology* 2003; 28(8):1546–1552. 3. Carmen B, Angeles M, Ana M, Maria AJ. Efficacy and safety of naltrexone and acamprosate in the treatment of alcohol dependence: a systematic review. *Addiction* 2004; 99(7):811–828. 4. Mark TL, Kranzler HR, Poole VH, Hagen CA, McLeod C, Crosse S. Barriers to the use of medications to treat alcoholism. *Am J Addict* 2003; 12(4):281–294. 5. Crabbe JC, Phillips TJ. Pharmacogenetic studies of alcohol self-administration and withdrawal. *Psychopharmacology (Berl)* 2004; 174(4):539–560.

8. The Nordic Poisons Network

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The Nordic region consists of five countries, Denmark, Finland, Iceland, Norway and Sweden, with an aggregate population of about 24 million. The first Nordic poison information centre was established in Sweden in 1960, with Finland and Norway following in 1961. The Danish centre started in 1972 and the Icelandic in 1994. Today all centres are publicly funded and provide 24 hr telephone service to the whole country. All operate from a hospital but are not responsible for treating patients.

The centres in Finland, Norway and Sweden answer calls from the public and health care professionals and currently receive about 750–800 calls/100,000 inhabitants yearly. The Danish centre only answers calls from doctors, and consequently receives slightly less calls. In the Danish centre calls are primarily answered by physicians, while in Finland, Norway and Sweden the staff taking calls mostly has a pharmaceutical training. The first formal meeting of the Nordic poison information centres was held in Stockholm on 31.10.1980 with representatives from Denmark, Finland, Norway and Sweden. The meetings were continued and in 1990 The Nordic Association of Poison Information Centres (NAPC) was founded during the 12th Nordic meeting in Stockholm. The goals of the Association are to promote co-operation and exchange of experience between the Nordic centres, to promote knowledge of the activities of poison information centres and the conditions for their activities and to co-ordinate contacts between Nordic poison information centres and authorities. The Nordic meetings, now held yearly, have continued with the 27th meeting to be held in Helsinki in September 2005. These meetings have become an essential part of the continuous professional education of the staff of the centres. Sharing of experience has proved especially valuable. Practice oriented topics like quality and preparedness issues have been discussed in educational formats giving all types of personnel a chance for exchange of experience with their respective peer groups. Other forms of Nordic educational activities include the bi-annual Nordic Course in Clinical Toxicology, which will be held for the 7th time in Denmark in 2005, and distance learning activities like the Nordic e-mail cases. Active continuous informal contacts between the Nordic centres include exchange of information on products, discussions on problematic cases, and of problems related to availability of antidotes. Due to similarity of the societies of all Nordic countries, benchmarking made possible by the network can be used to promote national poison information centres. The Nordic network is working to facilitate establishment of poison information centres in the Baltic states.

9. A Network Within a Network—Society of Clinical Toxicology of German, Austrian and Swiss Poisons Centres

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History: The Society of Clinical Toxicology was founded in Munich, December 1985 by 16 members under the name of ''Working group of Poisons Centres'' (''Arbeitsgemeinschaft der Giftnotrufe e.V.—AGGN''). During the first years, under the presidency of Prof. Max von Clarmann, the society fought mainly for the upkeep of the 15–20 years old poisons centres (PCs) in Germany. After 1990, during the chairmanship of Prof. Thomas Zilker, the history of the German PCs was characterized by a fundamental restructuring of these institutions due to a revision of the German Chemical Law. During that time the number of PCs in Germany was reduced from 20 to 10 centres, while the equipment and staff was enhanced by the national research project ''EVA,'' supporting the recording and analysis of poisoning cases, sponsored by the Federal Ministry for the Environment, Nature Conservation and Nuclear Safety. Two new PCs (Erfurt and Göttingen) were founded. The period from 1998 under the presidency of Prof. Sacha Weilemann was characterized by intensifying the cooperation between the PCs, particularly the contact to the Vienna PC was extended. In 1990 the statutes were revised and the association was renamed ''Gesellschaft für Klinische Toxikologie e.V.'' (''Society of Clinical Toxicology,'' a registered and nonprofit society) enabling a better integration of the PCs into the field of clinical toxicology. Since June 2003 the fourth generation of executive committees coordinates the activities of the society. *Objectives:* The Society of Clinical Toxicology is an association of physicians and natural scientists working in a poisons centre, in the fields of clinical toxicology or analytical or forensic toxicology. It acts to guarantee helpful consulting of the general public and the doctors in charge in the case of poisoning, thus optimizing medical service in poisonings for the population. It fosters the interdisciplinary relations between chemistry, pharmacy, informatics and medicine in order to improve the comprehension of clinical toxicological issue. It collaborates with international organizations (e.g. EAPCCT). *Members:* The 10 German, the Austrian and the Swiss PCs are represented by at least one and up to seven members. During the last 2 years the number of members has doubled. Half of all members are working actively in 4 working groups. *Working Groups (WGs):* At the general assembly in November 2003 six projects were discussed, prioritized and four WGs were initiated. 5 to 9 PCs are represented in every WG. Constituting meetings were held in January and February 2004. Names and objectives of these WG are mentioned below. *WG-I—Drug Monographs:* Preparation, updating and exchange of drug monographs in German language as a basis for consultation in acute poisonings in PCs. Well documented poisoning cases and current literature are taken into consideration based upon scientific standard and acknowledged procedures for quality assurance thus harmonizing the means of communication and consultation between the centres. *WG-II—Quality Standards in Poisons Information Centres:* Updating of quality standards according to the guidelines of the EAPCCT and including documentation of the necessary

resources of the PCs. Working on the interface between PCs, legislation and politics. *WG-III—Cooperation with Mycologists:* Updating and distribution of the mycologists' addresses for the use in German PCs when consulting acute mushroom poisonings. *WG-IV—Lethal Poisoning Cases:* Annual analysis, evaluation and publication of all the lethal poisoning cases in Germany, Austria and Switzerland which have been documented by the poisons information centres. Comparison with national mortality databases. Harmonization of poisoning documentation in PCs. During the last 14 months 13 meetings of the WGs were held in different PCs. Currently these four groups are experiencing a very high workload. *Homepage:* A new Homepage was built up in June 2003, based on a content-management-system, as a common virtual file with all meeting dates, team mailing lists, protocols and all relevant documents for each WG. For more information please contact: www.klinische-toxikologie.de. *Meetings:* Since 2003, the annual quality assurance meeting of the german-speaking PCs in autumn is linked with the general assembly of the society. Objective of these meetings is to reach a consent in therapy recommendations for poisonings as well as quality assurance in poisons information, treatment and documentation of poisonings. The next meeting will take place in Freiburg at 10-th and 11-th of November 2005. More information is available at: www.klinische-toxikologie.de/v2/index.php?id=6. *Results and Future:* In 2005 the first results of the WG activities will become available for use in the PCs. *WG-I:* A first standardized version of a drug monograph form inclusive definitions is now available and the WG has started to test this form and structure by creating first drug monographs. *WG-II:* After a first meeting with the responsible politicians in March 2004 the WG developed a preliminary version of the document ''Tasks of the Poisons Centres'' on request.[1] This list constitutes the basis of political discussions on the activities of PCs and was updated in December 2004. In 2005, the WG will implement the connection of the network of PCs with the intended Pharmacovigilance Network in Germany. Experiences of the Swiss and Austrian PCs support these activities. *WG-III:* The first common and updated list of mycologists is provided in all PCs for the impending mushroom season. In 2005 the WG will document the procedures for future updating and sharing of the list. *WG-IV:* All fatal poisoning cases of the year 2003 from 10 out of 12 PCs were collected and will be analysed and published in 2005. By implementing a standardised input table for the collection of information the WG has introduced a system of harmonisation of case documentation. As the synergy effects within the WGs are now apparent the common database will be used for collecting the information on the cases in WG-I (analysis of drug poisonings for the preparation of drug monographs) and in WG-IV (collection of fatal poisonings). After extensive preparatory works the WGs are now ready for a cooperation on a European level.

10. Key Activities of Selected Poison Centers in Poland and Baltic States—Pilot Study

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Introduction: Committee of EAPCCT for Eastern European Countries was established to develop better relationship between Poison Centres (PC). Results of EAPCCT survey were presented in 2003. The collected data suggested that detailed analysis of PC key activities and needs should be performed. The aim of this pilot study is to understand the morbidity and mortality rates associated with poisonings in populations served by 3 PC—Kraków (Poland), Vilnius (Lithuania) and Riga (Latvia). *Materials and Methods:* Retrospective data was collected from local publications as well as gathered in interviews with PC Directors. Data was analysed by the first author. Kraków PC—the 2002 and 2003 analyses include: data for adult (above 14 y) poisoned patients treated at the Department of Clinical Toxicology; all deaths at the scene of poisoning which were subject to post-mortem toxicological examination at the Department of Forensic Medicine in; data from enquires to poison information service. Vilnius PC—the analysis includes: adult patient data from the entire country who were treated in Vilnius Emergency Hospital; incidence of specific poisonings, in-hospital and out-of-hospital mortality data from all Lithuanian Health Care institutions (provided by Lithuanian Health Information Centre). Riga PC—the analysis includes: data related to patients treated in the Clinic of Intensive Therapy and Toxicology; data related to calls to Poison Information Centre; data for out-of-hospital fatal cases provided by the State Agency of Forensic Medicine. There is no currently established PC in Estonia. *Results:* Kraków PC—in the Department of Clinical Toxicology 4116 (M 66.1%, F 33.9%) poisoned Kraków adult inhabitants were treated in 2002 and 4341 (M 65.7%,

[1] www.klinische-toxikologie.de/v2/fileadmin/DOKUMENTE/ARBEITSGRUPPEN/AG-II/GFKT_AG-II_06_Aufgaben%20der%20GIZ.pdf.

F 34.3%) in 2003. The incidence rate per 10,000 adult inhabitants of Kraków was 63.1 and 66.5 respectively. In both years the most frequent cause of hospitalisation was acute ethanol poisoning, ethanol abuse by alcoholics and severe withdrawal syndrome (46% and 49.1%). Single ingredient ingestions, mixed and/or co-ingestions with ethanol were medicines 28% and 25%; carbon monoxide 5.2% and 6.2%; pesticides 0.3%; ethanol substitutes (methanol and ethylene glycol) 0.2%. The mortality rate was 0.3%. There was no substantial difference between a number of poison related fatalities out-of hospital in the years analysed—126 (ethanol 64.3%, carbon monoxide 16.6%) deaths in 2002 and 121 (ethanol 60.3%, carbon monoxide 23.1%) in 2003.The poison Information Centre recorded 1606 telephone enquires (71% health professionals, 28% general public) in 2002 and 2154 (62% health professionals, 36% general public) in 2003. About 35% of enquires were related to children. Vilnius PC—in the Republican Toxicology Centre, located in Vilnius University Hospital, poisoned adults from Vilnius and the most severe cases from the entire country are treated. The number of treated cases rose from 1375 in 1993 to 3203 in 2000, with a subsequent decrease (eg. 2639 in 2003). Mortality rates for treated patients varied from 7.5% in 1993 to 1.6% in 1999 and 2.4% in 2003. Most deaths (28%) occurred on the first day of treatment. In 43% of patients ethanol and its substitutes (methanol and ethylene glycol) were the cause of death. Lithuanian Poison Control and Information Bureau began its activity in 2002, 800 to 1200 calls per year are recorded, approximately 1/3 were paediatric cases. According to the data collected by Lithuanian Health Information Centre the total number of poisonings with chemicals in entire Lithuania has fallen from above 6700 (children under 14 ys—37%) in 1995 and 1996 to 4900 (children under 14 ys—17.3%) in 2003. Total number of fatalities caused by poisonings, both hospital and pre-hospital, has decreased from 1125 in 1995 to 628 in 2002. The most frequent cause of death was alcohol and its substitutes (app. 66%). Riga PC—the Clinic Intensive Therapy and Toxicology unit treats mainly adult poisoned patients from Riga. The number of treated cases increased from 2967 in 2001 to 3432 in 2003 (app. 64.8% male and 35.2% female). Ethanol and benzodiazepines were most frequent toxic agents. A mortality rate of treated cases was around 1.2%. The Poison Information Centre was founded in 1993. In 2002 it recorded 5475 calls, in 2003—4385, about 26% were related to children. The majority of enquires were from the general public (54%), with 39% from health services. Medicines were the most frequent toxic agent in enquires (48%). The number of prehospital deaths were collected by the forensic medicine department, in 2002—603 and in 2003—620 people died at the scene of poisoning. In 2002 42% of fatalities were due to carbon monoxide, 30.2% ethanol, and 9.2% opiates and other agents were the cause of death. In 2003 the number of deaths causes by ethanol increased to 48%, and for carbon monoxide fell to 37%. *Conclusions:* Although the methodology of data gathering was different for each country a consistent conclusion is drawn that poisonings are an important health problem in the CEE countries examined. The number of fatal cases suggests room for improvement in reaction time and need for wider availability of speciality toxicological information to all health professionals. The promotion of preventive measures by means of education and increasing information availability is an important role for PC's to fulfill. The number of calls answered by poison information services proves that there is a substantial demand for professional expertise in the field of toxicology in these countries.

11. Models and Networks in Italy for Antidotes Availability and Supply in Emergency Settings

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Background: In the last ten years, increasing attention has been paid to the unavailability of antidotes in hospital pharmacies and emergency departments (EDs). The situation is not confined to selected geographical areas: essential antidotes are not adequately stocked in many European and extra-European countries. *The Italian Situation:* The Pavia Poison Center (PC) was asked by the National Institute of Health to conduct a survey in order to define the Italian situation concerning antidotes availability in emergency setting and to identify areas of possible improvement. A questionnaire was mailed to Pre-Hospital Emergency Services (118 s), EDs, Intensive Care Units (ICUs) and PCs of all Italian hospitals, who were asked to report the amount currently in stock of 77 different antidotes and selected drugs used in the management of poisoned patients. Insufficient antidote stocking was defined as lack of the antidote or an amount inadequate to treat 1 seriously poisoned 70-kg patient for 24 hours. Antidotes such as glucagon, hydroxocobalamin and fomepizole were stocked only in 1 out 193 EDs who responded to the survey; other essential but less expensive drugs such as ipecac syrup, activated charcoal and flumazenil were lacking in 39.4%, 13.5% and 6.2% of EDs. Hospitals receiving educational courses in clinical toxicology by PC staff in the previous five years were stocking antidotes more appropriately. *Models and Networks:* According to the study results, subsequent actions were addressed to improve both educational and organizational aspects. Educational activities implemented by Pavia PC included the Basic and the Advanced Course in Toxicology (B-Tox and A-Tox, respectively), as well as monothematic seminars on most common and/or severe toxicologic emergencies. Every year, more than 20 educational activities were

performed all over Italy. Organizational aspects were approached at three different levels, involving hospitals, industries and national Authorities, using three different models implemented by the Pavia PC. The hospital network for antidotes involves all hospital departments participating in the above mentioned survey. Information on antidotes stocks were included in a national database (BANDA) accessible through our PC website (www.cavpavia.it), and are now updated at least twice a year by every hospital. Information in the database is available for all registered users: in case of need, a simple query allows to identify hospitals provided with the antidote looked for at local, regional or national level. Moreover, this information can be used to ameliorate antidotes procurement by hospital emergency services, through agreements with other hospitals serving the same area. At industrial level, a second network of antidotes stockpiles was implemented in chemical plants. Antidotes were supplied according to specific risks in single plants, as well as antidotes for pre-hospital management of fire victims. Antidote stocking and replacement was considered a PC responsibility. In order to avoid antidote misuse, in the operating procedures it was clearly stated that antidotes have to be used under the advice of the PC physician both in pre-hospital and hospital setting. Special attention was addressed to make sure the antidote is available for 118 s physicians and/or is brought to the ED with the patient. Local 118 s, EDs, ICUs and hospital headquarters were repetitively mailed and kept updated with the activities accomplished. This unique procedure allows a timely and proper management of cases of acute occupational poisoning; moreover, through PC intervention, antidotes may be available for other cases of poisoning presenting in the EDs of the hospitals close to the plants. A third national network is actually operating within the context of an agreement between the Italian Department of Civil Protection and the Pavia PC, realizing the national antidotes stockpile for NBCR emergencies. Acknowledgments: Supported by grants from the Italian Ministry of Health—National Institute of Health, the National Research Council and Italian Department of Civil Protection.

12. Development of Poisons Centres Around Europe—A Comparison Between Eight European Centres

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Objective: In order to exchange experience and to learn from others to improve the Norwegian Poisons Information, 8 different Poisons Information Centres (PICs) in the middle and northern part of Europe were visited and studied in 2004. *Methods:* 8 PICs in 7 different countries were selected to cover different organisations, cultures and sizes. In Great Britain, one large (London) and one small centre (Cardiff) were visited. The PIC in Munich was selected as a representative for Germany and that in Lille for the French PICs. Otherwise the only PIC in Switzerland (Zurich), Belgium (Brussels), the Netherlands (Bilthoven) and Sweden (Stockholm) was studied. 1–2 days were spent at each PIC. The gathered information was based on a completed questionnaire, discussions and own observations. The following topics were focused: Organisation and funding of PIC, main tasks and customers, staffing and competance, number of calls and type of service. In addition, the database systems were particularly studied. *Results:* The PIC in Switzerland was organised as a private charity foundations, otherwise the PICs was funded directly or indirectly by governmental budgets. In Great Britain and in Munich the PIC was part of a toxicology unit, also comprising beds and laboratory facilities. In Great Britain and the Netherlands the PICs were only opened for health personnel. All offered 24 hours telephone service, which was regarded as their main function. All PICs were also involved in preventive work (5–20%), while research and elucidations counted for a small and varying part of the work. The total number of employees varied from 17–37 people. In Brussels, Lille, Zurich and Munich, only medical personnel were routinely answering the phone as first line. In Sweden, Great Britain and the Netherlands pharmacists, biologists, and nurses on BSc or MSc were the first line duty. All PICs had a second (or third) back medical duty. The part the first duty staff spent on telephone service varied from 100% (Switzerland) to 50% (Sweden). The work was more specialised on the continent than in Great Britain and Sweden. The number of calls per 100,000 inhabitants varied significantly between centres, from approximately 200 in Munich to 850 in Stockholm. Inquiries regarding drugs in general, environmental toxicology and teratology were handled quite differently from centre to centre. Follow-up of patients was only done in hospitals in Switzerland and partly done in Great Britain. The practise of collecting and evaluating documentation on chemicals and drugs varied a lot from one PIC to another. All PICs had own developed electronic data bases. Direct electronic recording of the inquiries were done in the majority of the centres. *Conclusion:* The 8 PICs studied had mainly the same tasks, but organisation and staffing have been solved differently. In some countries the telephone is only serving health personnel and not the public. Another characteristic feature is the different number of calls per 100,000 inhabitansts. The quality of most PICs should be increased and all the resources within PICs could be better used by more collaboration and harmonzation in Europe. One way to proceed is to elaborate regulations about the existence and role of PICs within EU. EAPCCT should be a driver in this process.

13. The Collaboration Between the BfR and the German Poison Control Centres

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Background: One year after the establishment of the first European Poison Control Centre (PCC) in Paris, the first German PCC was created in the former German Democratic Republic (GDR) in 1960. The Federal Republic of Germany (FRG) followed soon with the West Berlin Centre in 1963. For a long time, it was the centre consulted most frequently in Germany with a specialization on calls in cases of poisoning involving children. The former GDR centralized the toxicological information service in the GDR Institute of Drug Control in 1981, whereas the federal structure of the FRG resulted in a number of 17 centres in 1992. The PCCs are established under the responsibility of the German Länder. Most of them are part of or closely related to University Hospitals and 3 of them have Intensive Care Units for treatment. In 2004, the PCCs handled more than 150 000 poison information calls with a follow-up rate of about 30–40%. In 1964, the foundation of the European Association of Poison Control Centres (EAPCC) gave the impulse for the German Federal Ministry of Health to give a mandate to the German Federal Health Office (BGA) for the implementation of a Poison Information Database similar to the database of the US National Clearinghouse for Poison Control Centres. In 1965, a BGA Commission ''Identification, Prevention and Treatment of Poisonings'' was assigned. In 1980, the Poison Information Database has been supported by electronic data processing via the German Institute for Medical Documentation and Information (DIMDI) with the databases ''Giftpool'' and ''Indexline.'' *German Toxicological Network:* The risk documentation for poisonings has been supported by German legislation on chemicals. In 1982, the foundation of the Chemicals Act was laid by a systematic assessment of 1. old compounds (ca. 100,000) through an advisory board and 2. new compounds by joint assessment based on animal study data from German Federal Institutes. In 1990, compulsory notification of cases of poisoning by attending physicians was introduced to document all human health impairments by exposure to chemicals. In addition, all German PCCs have to report their findings with regard to cases of exposure to the Federal Institute as well. For proper risk identification, the German manufacturers have to report the formulations of chemical products to the product data base of the Federal Institute, which in turn provides for the product data bases in the PCCs. These activities were assisted by two research projects of the Federal Ministry for the Environment, Nature Conservation and Nuclear Safety (BMU): Firstly, with a harmonized case data collection (Project EVA) and secondly, with the improvement of the electronic product data collection and exchange between industry, PCCs and BfR (Project TDI). *Cooperation:* In 2004, the toxicological network consists of ten German PCCs, more than 5000 manufactures, distributors and importers (most of them are organized in the German Association of Chemical Industries—VCI) and the BfR. In parallel to the documentation of cases of poisoning in the PCCs, a second monitoring and documentation system was established in 1990 at the BfR because the German physicians are obliged to report cases of poisoning and other health impairment caused by chemicals, chemical products or environmental factors to the Federal Institute. Physicians have to report their findings after their treatment has been finished. Also cases of suspected poisoning have to be submitted. The network is growing: progressive computer technology and similar working conditions have led to a sufficient data exchange. The Federal Institute is the core of the German toxicological network. Physicians and PCCs report human data of poisonings to the BfR case database. Every case is assessed including the chemical product involved with its detailed formula provided by BfR product database containing the notification by the German manufacturer. The information contained in the product database is regularly submitted to the PCCs. Data of cases of poisoning in humans are condensed in a harmonized and standardized data file for analysis. Parallel cases of special toxicological and scientific interest are prepared for standardized case-reports. *Main Fields of Work 1990–2004:* 1. The development of instruments for documentation and evaluation of cases of poisoning. This includes particularly the assessment of the causal relationship between exposure to a chemical substance or product and manifestations of a disease. For a better retrieval, a bilingual case report database (Project Case-DB) is implemented in the BfR also with the support of the German Federal Ministry (BMU). 2. Evaluation of health impairments by certain compounds with focus on specific compounds and circumstances. 3. Assessment of health impairments caused by chemical substances in the environment, especially from industrial accidents 4. As a consequence of documentation and evaluation of health hazards, a ''toxicovigilance'' procedure for rapid information of industry, ministries and industrial associations on health risks of products on the basis of immediate and summarised reports has been established. For severe cases of toxic effects in humans, producers—as well as responsible authorities and ministries—are directly informed and asked for risk-reducing measures (PRINS-System). *Conclusion:* The data obtained by good collaboration between BfR and the German PCCs with a systematic human data collection are more suitable for human risk assessment than only data from animal experiments. Although the case documentation of this spontaneous reporting system does not give a representative overview of human health hazards, it serves as a proper basis to propose hypotheses and preventive measures. It helps to initiate single risk-reducing activities and perform additional studies for a better characterization of the circumstances and to control the effects of risk-reducing measures. Some of these have already been reported and discussed at EAPCCT conferences.

14. Colchicine Poisoning. A 5-Year European Poisons Centres Survey

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Background: Colchicine, an alkaloid occurring in the meadow saffron (*Colchicum autumnale*), is used to treat gout and familial Mediterranean fever. Poisoning, be it from ingestion of meadow saffron leaves or from colchicine tablets, is a rare but regular medical emergency. Information about morbidity and mortality of human colchicine poisoning in Europe is virtually absent. Treatment of colchicine poisoning is supportive, the effectiveness of which is very limited in severe cases. The ingestion of >0.9 mg/kg usually results in a fatal outcome. Immunotherapy with anti-colchicine antibodies (Fab-fragments) was available on an experimental basis in the 1990s. The aim of our study was to collect data on colchicine poisoning during a 5-year period from European Poison Centres (PCs). *Methods:* An European survey was performed in October 2004 sending an e-mail to 80 European PCs in 33 countries using the EAPCCT Poison Centre directory. The PCs were asked to report the overall number of human colchicine poisoning cases during the years 1999–2003, the number of fatal cases, and the respective number of colchicine tablet and *C. autumnale* poisonings. *Results:* By November 20, 25 PCs in 14 countries had responded. They reported 355 cases of colchicine poisoning, 15 with a fatal outcome (fatality rate 4.2%). 7 PCs (28%) reported no case. The remaining 18 PCs reported an average of 20 cases (range 1–53). In 119 cases (34%), ingestion of *C. autumnale* material was involved (only 1 report with no information about the source of colchicine, i.e. plant or tablet). If the remainder of the PCs reported a similar pattern for their cases, this would lead to an estimate of 1100 cases with 45 fatalities per 5 years. *Conclusions:* Colchicine poisoning occurs in most European countries with a low incidence, but is more abundant in areas where poisoning from *C. autumnale* is more frequent. Colchicine poisoning has a high fatality rate. As supportive treatment is limited due to the mechanism of toxicity, ready availability of anti-colchicine antibodies would be highly desirable. This is particularly true due to the fact that colchicine is readily accessible for use as a biological weapon in terrorist attacks. The EAPCCT is able to act as a conduit for quick internet-based surveys among its members, a procedure which proved effective on several occasions.

15. Harmonized Multicentre and Multinational Data Collection of Fatal Poisoning in 2003

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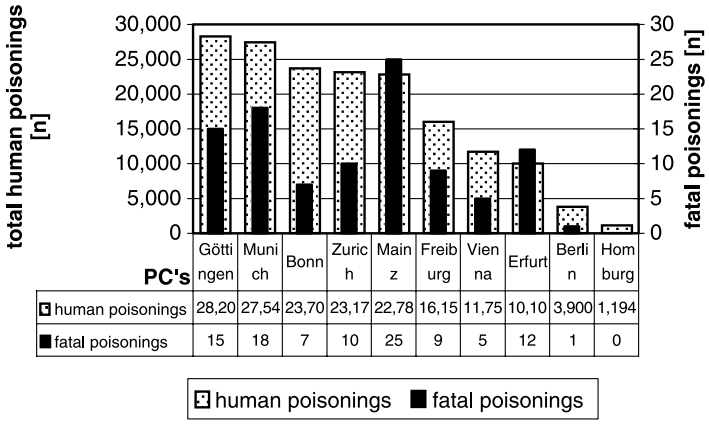
Objective: Analyses of cases of fatal poisonings are important to determine the most dangerous products and substances, and therefore for poisoning prevention. Poison Centre's (PC) data can be particularly helpful in this purpose. Multicentre studies are necessary because of the small number of fatal poisonings recorded at each PC. The Society of Clinical Toxicology of German speaking countries (Gesellschaft für Klinische Toxikologie) has instituted working groups to support networking of German, Austrian and Swiss PCs and to promote the harmonization of operation processes in PCs. The goal of one of the working groups is to collect, evaluate and publish cases of fatal poisoning. *Methods:* Harmonization of data sets was agreed and frame data were tabled in a standardised way. Data on fatal poisoning were collected in all PCs for the year 2003. Data on callers, circumstances, age groups and route of exposure were further adjusted to agreed definitions. Then the data sets were pooled and evaluated. *Results:* Data from 10 of 12 PCs were available. The data pool is characterized in Table 1. The 101 cases of fatal poisoning with a sufficient causal relationship between exposure and symptoms were further analysed. The fatality rates were different between

TABLE 1

	Total of human poisonings	Total of human fatalities recorded	Fatalities related to poisoning	Fatality rate
Total (all PCs)	168,514	168	101	0.6%



PC's	Göttingen	Munich	Bonn	Zurich	Mainz	Freiburg	Vienna	Erfurt	Berlin	Homburg
human poisonings	28,20	27,54	23,70	23,17	22,78	16,15	11,75	10,10	3,900	1,194
fatal poisonings	15	18	7	10	25	9	5	12	1	0

FIG. 1. Relation between total human poisonings and fatal poisonings of each centre in the year 2003.

PCs (Fig. 1). The number of fatal poisonings is not correlated to the total number of poisonings recorded in the PCs, but rather to the follow up rate of a particular centre. The majority (69%) of the fatal cases are adults (>=18–<65 y), 25% are elderly patients (>=65 y), 5% are adolescents (>=14–<18 y) and in 1% the age is unknown. No children (0–<14 y) were concerned. Male gender outweighed females with 48% (37% women, 15% unknown), and suicides dominated with 74%. 54% of the deaths were caused by pharmaceuticals, 23% by pesticides, 6% by chemicals, and 5% by drugs of abuse. The 3 most common lethal substances, representing a fifth of all fatalities are parathion (n=11), amitriptyline (n=5) and trimipramine (n=4). *Conclusion:* For the first time in the 40 year history of PCs in Germany, Austria and Switzerland, a systematic data collection of fatal poisonings was performed. The data provide information for risk assessment and prevention in clinical toxicology. The harmonization process and data collection will be continued in the future. This project could extend to other European countries creating a nucleus for European PC data pooling.

16. The Work of Poison Centres and Clinical Toxicology Information in Regulatory Risk Assessment

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Health risk assessment procedures are aimed to reduce risks from exposure of humans to a variety of substances, particularly chemicals used in households, hobby products, as biocides, from food consumption, as well as from microbial contaminations. Risk assessment is performed by comparing toxic doses with doses revealing from contacts with those chemicals (=exposure). Toxic effects are normally studied by animal experiments, and to a growing extent, by in vitro testing. For extrapolation of animal data to humans, so called uncertainty factors are used, normally one factor of ten for consideration of interindividual and another ten for intraindividual variability. For regulatory purposes of classification and labelling of substances, this approach is appropriate, however, to describe the current situation of health effects in humans, and to get control about incidences of illnesses due to contacts with chemicals, data from human health impairments are needed. Besides a small number of controlled trials in humans the majority of information about human health effects related to exposures to chemicals, information must be taken from poisonings and other incidental con-tacts of chemical substances leading to acute or chronic health impairments. In which way can poison centres and other institutions collecting data about human health effects support the regulatory work of risk assessment? This question has been discussed in the last years on a number platforms, particularly by WHO/IPCS. To consider poison centres for risk assessment procedures, the needs of risk assessors and the facilities of poison centres should be analysed. First of all, thousands of substances must be considered for risk assessment. In the European Union, the new chemicals policy (REACH approach) has introduced a paradigm shift by notifying a number of up to 30.000 substances which have to be evaluated by a surveillance system that controls occurrences of health impairments introduced by chemical exposures. Also, priority setting has become an important role for the REACH regulation, because many chemicals are not sufficiently toxicologically tested. Statistics of poison centres can be taken to analyse the frequencies of contacts of humans with chemicals. Although poison centres have an overview for contacts leading primarily to acute intoxications, the incidences of calls in PC's may be indicative for exposure frequencies in general. The BfR had shown recently that PC's may contribute to such a system: a

list of substances, revealed by an analysis of chemical products, were analysed by means of frequency analyses of poison centre calls. All substances were toxicologically classified and their importance for an assessment was also evaluated by expert judgement. A principal component analysis balancing frequencies with toxicological data separated substances having low from those having high priority. Secondly, evaluations of manifest poisonings documented by approaches of scoring poison severity can provide information additionally about the hazards from chemical exposures. In the 2002 statistics of the PC Göttingen, 36% of all calls referring to chemical products had symptoms, with different levels of severity. Thirdly, further selection of those cases may support data about human poisonings to characterise important types of toxicological effects in humans, e.g. systemic (e.g. cardiac or neurologic effects) or local (e.g. corrosive) effects and their frequencies. Because poison centres may have differing work priorities (e.g. children, workers, internal medicine, general pharmacology) their impact to support health effect assessment differs accordingly. With the help of PC classification and labelling of paraffins could be managed from human data due to aspiration toxicity. Also, benzene has been classified and labelled according to epidemiologic studies in workers in leather industry. However, the work of poison centres is primarily focused to acute effects in humans. Therefore, other projects, networks and institutions that are aimed to chronic effects of substances in humans have to be included.

17. Professional Societies and Evidence-Based Toxicology

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That healthcare should be based on the best information we have is so axiomatic that it may seem that it need not be stated. However, the history of the epistemology of medical wisdom demonstrates that until recent times this there has been a conspicuous gap between our concepts of optimal medical practice and the data supporting, or in many cases refuting, such practices. Few would not agree that a full and critical evaluation of all of the issues necessary to transform clinical practice from anecdote and ''collective tribal wisdom'' to that based on true empirical determined information is our obligation. However, such exercises are intellectually demanding and extremely time consuming. Thus it is unreasonable to expect that individual practitioners will make these determinations on the many potentially important aspects of their practice. It therefore falls on our professional societies to take up these deliberations and thus provide guidance to their members. In the case of clinical toxicology the joint position statements issued by the European Association of Poisons Centres and Clinical Toxicologists and the American Academy of Clinical Toxicology on gastric lavage, syrup of Ipecac, whole bowel irrigation, activated charcoal, cathartics, and urinary optimization are emblematic of the very high quality kinds of results that can derive from the activities of our professional societies. Having accomplished the production of important position statements, and subsequent changes in clinical practices, that can be directly related thereto it is inevitable at this juncture that as societies we ask where we go from here? Generally the position statements of our societies have dealt with acute care and certainly that characterizes the important joint documents to which I have alluded. There is little question that there are a multitude of additional acute care questions, which can be addressed through similar exercises. However, the focus of clinical toxicology societies should be sufficiently broad to also encompass those issues that deal with the question of occupational and environmental exposures, chemical carcinogenesis and more subtle toxic effects. The proliferation of misinformation on non-peer reviewed Internet sites, often fueled by trial lawyers, has provoked a toxic hysteria about certain issues that results in substantial unnecessary concern about non-validated allegations of harm from various chemical exposures. For example, today's toxicologic landscape prominently features great, and unjustified, concern about issues such as mercury toxicity from dental amalgams, the induction of autism spectrum disorders from thimerosal in vaccines, toxicity from ''toxic mold'', and idiopathic environmental intolerance (multiple chemical sensitivity syndrome), to name just a few of the more egregious examples. It is also important that professional societies offer guidance on such diverse issues as the relevance of rodent studies to the assessment of human carcinogenesis, air pollution and human pulmonary disease, or the appropriate exposure limits of arsenic in drinking water. The list of toxicologic questions with important implications to human well being is prodigious. For our professional societies to critically evaluate these kinds of issues requires that they incorporate the most rigorous and accepted methodologies, similar to those used in the generation of the joint position statements. However the methodology for these nonacute types of analyses is vastly different. For nonacute health endpoints we are faced with the dilemma of assessing health problems that may have substantial baseline prevalence in the general population. Thus establishing a nexus between a chemical exposure and a disease process in the population requires that a demonstration of a causal relationship between the exposure and the disease actually exists. Most often this is investigated initially by observational epidemiologic studies. Only rarely do we have data on these kinds of health endpoints from the preferred prospective controlled randomized interventional clinical trials. When the latter are correctly designed, executed, and analyzed, endpoints that are clearly more common in the treated group can generally be considered to

be ascribed to the effect of treatment. However, such surety cannot derive from observational studies. Observational studies provide only evidence of statistical association; never cause and effect relationship. It is certainly not the leaves falling off trees that cause winter to come despite the extremely impressive statistical association. While the absence of a statistical association, particularly if in several well controlled, appropriately designed, and correctly analyzed epidemiologic studies, implies evidence for a lack of a causal nexus between the exposure in question and the disease under study, the presence of such an association can never be taken to conclude that such a causal relationship exists. One only needs to look at the opposite results obtained from observational studies of hormone replacement therapy (HRT) and the interventional clinical trials on this topic to realize the potential limitations of the former. This example is made even more poignant by the fact that the observational clinical trials on HRT were large and extremely well done. The necessary formalism to pursue to determine if a statistical association seen in an observational study truly represents a causal nexus between a chemical exposure and a disease condition was developed over 50 years ago in the analysis of Austin Bradford Hill's observation, along with Sir Richard Peto and Sir Richard Doll, observations of a statistical relationship between cigarette smoking and lung cancer in observational studies. Following the recognition of this statistical association an analysis was carried out using the criteria articulated by Hill, primarily in his presidential address to the Royal Society of Medicine in 1965. These criteria represent the number of factors that need to be considered in determination of whether a statistical relationship represents a true causal one. The factors constituting the components of these criteria and some observations concerning their use are provided below. *1. Strength of Association:* This criteria refers to the presence or absence of a statistically significant association between the exposure and the disease process under study; *2. Consistency of the Observational Studies:* In evaluating observational studies, given their limitations, it is of great importance to confirm that the association seen is replicated in various populations using different study types; *3. Specificity:* There is no such thing as a general toxin. Rather substances cause specific diseases under specific circumstances of dose and exposure. Thus it is important that the disease in question be specific and that the analysis bears this specificity in mind. Thus, for example, an animal study showing that a substance can cause lymphoma in rodents is of no value in considering the importance in a observational study of a relationship between exposure to that substance and hepatocellular carcinoma; *4. Temporality:* This is probably the single component of the Hill Criteria which must be considered to be inviolate. The disease process in question must follow the exposure; *5. Dose-Response:* A statistical association becomes a much more credible causation theory if it can be shown that there is a distinct gradient with increasing exposure causing greater likelihood of disease; *6. Plausibility:* This is perhaps the weakest of the Hill Criteria. Plausibility refers to the range of possibilities that may explain why an exposure could conceivably cause a disease. Probably the single most important component in fulfilling the plausibility criteria is intellectual creativity, not scientific probability; *7. Coherence with Other Scientific Studies:* This relates to the universe of scientific studies relevant to the topic. To be taken as a potential causal relationship the general universal scientific studies should be consistent with that relationship; *8. Laboratory Experimental Support:* This criteria probably most importantly relates to animal studies. However, other studies, such as in vitro studies may, at times, help fulfill this criteria. For example if the observational studies suggest a relationship between exposure to a substance and a carcinogenic effect and the substance in question is shown to be genotoxic in in vitro studies, this would be supportive of a causal relationship; *9. Analogy with Other Similar Circumstances:* This, like plausibility, is one of the weaker of the Hill criteria. Thus a well-defined and widely accepted methodological paradigm exists whereby our professional societies may bring the force of their collective intellectual wisdom to a broad range of toxin-related issues in our society.

18. Derivation of Clinical Decision Rules in Toxicology

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In the past two decades numerous problems have been subjected to clinical decision rule analysis. Clinical decision rules allow clinicians to increase their confidence that patients meeting specified criteria can be managed more efficiently without a loss of safety. While a variety of guidelines have appeared in the toxicology literature, there has been little application of an explicit clinical decision rule approach to derive or validate them. Many of our uses for decision rules relate to determining when the chance of adverse outcome related to an exposure has been reduced to an acceptable minimum and the patient may be discharged. One example is determining by telephone which children are not at risk following exposure and may be observed in their homes (a dichotomous decision). At the other extreme of care is determining when it is safe to discharge a victim of cyclic antidepressant overdose. Other decision rules may use a variety of factors to determine the likelihood of a particular outcome at defined clinical intervals to determine the application of expensive or invasive therapy (e.g. alkalinization or dialysis for salicylate toxicity). The biggest deficiency in the application of clinical decision rule derivation to medical toxicology has been

the dearth of input variable data and outcome data that is prospectively defined, relevant and complete in each case. Most of our past experience with rule derivation has been based only on retrospective poison center data including maximum possible quantity ingested and outcome that reflects incomplete follow up—with the assumption that ''if the outcome was really bad, we would have heard about it''. Other management decisions are based upon retrospective evaluation of small hospital series including mixed overdoses and inadequate validation or quantification of the ingestion. The derived rules in use have been relatively simplistic, often solely based on a single input variable, the estimated dose or a timed serum drug concentration. They have been derived by intuition rather than statistical methodology. This is not to say we have been unsuccessful—the management of acute acetaminophen overdose is a great success. But with the systematic, prospective collection or these and other inputs such as presence or absence of specific symptoms at given times post ingestion or specific serum concentration at a time after full drug absorption or effect, rules may be made more reliable and management more consistent. The derivation of a decision rule often uses multivariant analysis to determine which predictor rules provide independent information about the likelihood of an outcome. In the case of most decision rules for toxicology, in which we are more interested in sensitivity (avoiding bad outcome), than predicting the likelihood of a particular outcome (accuracy), recursive partitioning may be more helpful than logistic regression or discriminant function. One potential application of this process is developing a decision rule for triage of unintentional pediatric exposure to hydrocarbons in a developing country. The following describes the rule derivation process as applied to this application. In the developing world hydrocarbon aspiration is quite common due to the home storage of fuels for cooking, lighting and vehicles and the common use of containers that are not specific for fuels or designed to be childproof. Furthermore, local clinics are infrequently able to take care of more severe events or to transfer in a timely manner should severity develop. Transfers to higher level centers consume disproportionate resources in developing economies. Parents are resistant to unnecessary transfer. Clinicians are under pressure to avoid poor outcome but do not have a uniform approach. Clinicians need a guide to determine who may be safely discharged after a time of local observation and who is likely to need the resources of a higher level center. Variables for potential inclusion in the rule were prospectively determined, and with prospective data collection, subject to assessment of reproducibility (κ) in the population to which the rule is to be applied, by those expected to use the rule. Variables include respiratory symptoms at presentation and at timed intervals. Oxygen saturation and CXR are part of the data collected but may not find a role in a final rule if they are not uniformly available and consistently interpreted in a rural environment of potential use. Sample size was predetermined based on effect estimates and power calculation (and a minimum of 10 with each outcome per variable in the decision rule). The derived rule must involve only a few easy to assess inputs, be easy to use and provide safe allocation when judged in a two by two table (avoidance of unsafe outcome rather than perfect allocation or minimization of inappropriate referral). For rule inclusion it is expected that variables will have an intuitive association with outcome, be clinically ''reproducible'' (screened for κ), screened for inclusion by univariate association (relevance) and not to replicate discrimination provided by other variables (uniqueness). The relationship of individual variables with outcome will be explored. It is expected that derivation will involve multivariant analysis and recursive partitioning. Ultimately it is expected that the rule will be prospectively tested in a different population, by physicians specifically trained to use the rule (so the rule is assessed, not the skills of the users), but not those who derived the rule. The ability of the rule to successfully predict outcome (accuracy) will be assessed, along with inter-observer variability in reaching the key decision (discharge, observation, referral) and the ease of use. The rule will be modified (simplified if possible) and reassessed with a focus on determining the actual impact on practice and potential cost savings.

19. Indices to Assess Fatality and Morbidity of Poisoning: Application to Opioid Overdose

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Objective: To introduce more reliable indices for describing and comparing fatal and non-fatal consequences of drug overdoses, and illustrating these by applying them to pure opioid poisoning in Scotland. *Background:* An increasing frequency of opioid overdoses was reported in the 1990s in Scotland (1). Many studies have compared the number of single fatal poisonings with prescribing statistics to derive a fatal toxicity index (FTI) as deaths per million prescriptions (2,3). A major concern about using FTI is that it takes no account of the effect of the likelihood of taking certain drugs in overdose (4). In addition, FTI is not applicable to drugs which have illicit supply. Current approaches of comparing drug overdoses (not death) are based on relative likelihood; odds ratios or risk ratios (5). Ideally these need to be developed to derive an absolute measurement of the numerator of poisoning risk. *Methods:* Three new approaches were used to estimate risk of fatal consequence occurrence based on poisons enquiries, by telephone (Tel) or internet (TOXBASE, Tox) and hospital discharges (HD). We have used these to calculate FTIs

TABLE 1

Products	Tel-TMI/10^6	FTI/10^6	Tel-FTI/10^3	Tox-FTI/10^3	HD-FTI/10^3
Diamorphine	1851.5 (1347.1, 2454.3)	805.0 (488.7, 1235.5)	434.8 (265.6, 671.5)	84.0 (51.3, 129.8)	102.0 (62.3, 157.6)
Morphine	84.8 (52.0, 131.4)	63.6 (35.7, 105.3)	750.0 (419.8, 1237.0)	254.2 (142.3, 419.3)	1500.0 (839.5, 2474.0)
Methadone	29.5 (18.5, 42.2)	22.4 (13.1, 33.9)	760.0 (457.6, 1186.8)	181.0 (108.9, 282.6)	132.9 (80.0, 207.5)
Dihydrocodeine	55.5 (40.9, 73.6)	15.0 (8.0, 25.7)	270.8 (144.2, 463.1)	23.3 (12.4, 39.8)	61.3 (32.7, 104.9)
Codeine	22.8 (7.4, 53.3)	4.6 (0.1, 25.4)	200.0 (0.1, 1114.3)	10.9 (0.3, 60.6)	47.6 (1.2, 265.3)

based on these measures as well as prescription producing 4 measures FTI, Tel-FTI, Tox-FTI, and HD-FTI expressed per thousands. The exact 95% confidence limits were calculated. In addition a second set of measurements for evaluating risk of overdose was calculated using a similar methodology with the outcomes being an enquiry or a hospital discharge, related to prescribing volume. We have called these measures toxicity morbidity indices (TMI). To illustrate the applicability of this approach, prescriptions, poison risks and deaths from diamorphine, which has extensive illicit supply, were compared to codeine, dihydrocodeine, methadone and morphine from July 2002—to July 2003 in Scotland and Edinburgh. *Results:* FTI suggests fatality from diamorphine is significantly higher than other opioids (morphine, methadone, dihydrocodeine and codeine). The Tel-TMI suggests that non fatal consequences of diamorphine are also significantly more common. This shows that the higher FTI may be a result of higher overdose rates. By calculating Tel-FTI, Tox-FTI, and HD-FTI there is in general no difference between diamorphine overdose fatality and that with other opioids (Table 1). *Conclusions:* Well recognised weaknesses of FTI can be demonstrated by concurrent calculation of TMIs. They also can be addressed by calculating Tel/Tox/HD-FTIs for the same population. We suggest this integrated method of using FTIs and TMIs should be applied for epidemiological studies of overdose outcomes. *References:* 1. Bateman DN, Bain M, Gorman D, Murphy D. *QJM* 2003; 96:125–132. 2. King LA, Moffat AC. *Lancet* 1981; 1:387–388. 3. Buckley NA, McManus PR. *BMJ* 2002; 325:1332–1333. 4. Buckley NA, McManus PR. *Drug Saf* 1998; 18:369–381. 5. Bateman DN, Chick J, Good AM, Kelly CA, Masterton G. *EJCP* 2004; 60:221–224. *Acknowledgement:* Dr. Afshari is supported by a postgraduate education grant from Mashhad University, Iran.

20. Factors Influencing Poison Control Center Triage Decisions for Pediatric Ingestions

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Objective: To identify factors influencing decisions to refer patients to a hospital after ingestion of diphenhydramine or ibuprofen. *Background:* We established a poison control center (PCC) send-in guideline for pediatric diphenhydramine and ibuprofen ingestions with a threshold for referral to a health care facility (HCF) of >10 mg/kg and >250 mg/kg respectively. *Methods:* Retrospective case-control study using PCC case data from 2001 and 2002. Inclusion criteria: unintentional, diphenhydramine-only and ibuprofen-only ingestions, child <6 years old, call originated from home, management site ''Referred to HCF.'' Identical controls, except managed at home. Cases and controls were reviewed to determine: amount ingested, symptoms, caller characteristics (e.g. parent overly anxious), and product characteristics. *Results:* Of 1728 pediatric diphenhydramine ingestions, only 186 (10.8%) were referred to a hospital; of these133 met our criteria. Of 6497 pediatric ibuprofen ingestions, only 91 (1.4%) were referred to a hospital; of these 49 met our criteria. We reviewed 280 diphenhydramine and 118 ibuprofen cases that did not go to hospital (controls). Variables most commonly associated with risk of hospital referral for diphenhydramine were: amount ingested>send-in threshold (OR=2754, 95% CI 339–22347); product in bulk packaging (OR=6.3, 95% CI 1.4–28.5); and product in non-blister packs (OR=5.8, 95% 1.1–30.4). For ibuprofen, variables associated with risk of hospital referral included: uncertain amount ingested (OR=160.6, 95% CI 34.6–745.5); tablet in larger dosage form (OR=52.4, 95% CI 6.99–392.3); and caller characteristics (i.e. parent anxious) (OR=19.5, 95% CI

2.33–163.24). Presence of symptoms was a significant factor for both diphenhydramine (OR=1.9, 95% CI 1.05–3.44) and ibuprofen (OR=6.1,95% CI 1.8–20.4). None of the cases had severe outcomes. *Conclusion:* Pediatric diphenhydramine and ibuprofen ingestions were at greater risk of referral to a hospital if the suspected amount ingested was potentially larger than the send-in threshold. For diphenhydramine, bulk packaging and absence of blister packs were significant factors, while for ibuprofen it was uncertainty of amount, larger tablet dosage form and caller characteristics. This suggests an association between product packaging and the ability to determine the amount ingested by the PCC. Poison centers may consider including this information in poison prevention materials so consumers can consider the use of lower risk product packaging (non-bulk, children's tablets). PCC send-in guidelines for pediatric ingestions may be tempered by other factors (e.g. presence or absence of symptoms, caller anxiety) and the decision to refer should not be based solely on the amount potentially ingested. Send-in guidelines should be individually tailored by substance based on toxicity profile (onset, severity and nature of symptoms) and marketed products.

21. Poison Information Center Funding. . .What Are The Options?

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Objective: Most poison information centers provide emergency telephone clinical consultation, poison information and poison prevention education on a 24/7 basis. To provide this level of service, poison information centers are staffed by medical professionals who account for approximately 80% of a poison information center's expense budget. Adequate funding is essential to maintain quality uninterrupted poison information services. As a general principle, poison information centers are service entities and were not developed as profit centers. Consequently, most centers do not produce sufficient revenue to offset the expenses associated with the services that they provide; making poison information centers vulnerable to service reduction or closure when their host institutions or funding agencies seek ways to reduce expenses. When funding reductions loom, crisis management to resolve the impending financial shortfall prevails—sometimes the appeal is successful and at other times poison information centers fall victim to the 'bottom line.' The objective of this presentation is to discuss proactive strategies for diversification of revenue sources as a way to eliminate or reduce funding crises. *Discussion:* The elimination of reliance on single-source funding and diversification of revenue streams are the optimal approaches to secure long-term funding for the poison information center. To avoid funding crises the efforts must be proactive, continuous and innovative. Poison information centers must seek funding from the constituencies that they serve and also think beyond conventional service recipients for other sources of revenue. The traditional sources of revenue include funding support from the host institution and/or local, state and federal government. It is critical that those entities, such as government, who have provided traditional support be lobbied on a continuous and reinforcing basis with regard to the human and financial benefits associated with poison information centers. While these sources have provided stable funding for some centers, they have been the bane for other centers. To reduce financial vulnerability, poison information centers should seek complimentary revenue streams that may include engaging in contracts with hospitals in the service region (member hospitals), poison information and toxicosurveillance services for industry and using poison information center personnel to staff 'hotline' services that are unrelated to poison information. Hospitals in the poison information center service region are the beneficiaries of the center's patient care advice and should provide some support to the center. This may be in the form of an annual contract for service or a fee per call. While the sum generated from each health care facility may be modest, the total amount of revenue generated can be substantial. Implementation of direct patient charges to hospitals that do no participate in the member hospital program is another viable revenue stream. Business and industry have an ethical, medical and legal obligation to respond to consumers who have been exposed to one of their products. Poison information centers have the existing infrastructure to provide the 24/7 expertise that is needed by the companies and are able to do less expensively. Furthermore, poison information center data can provide industrial toxicosurveillance to enhance consumer and product safety. Additional expanded responsibilities include the provision of drug information on behalf of a pharmaceutical firm or a hospital or university that requires this service for its practitioners. Since health professionals staff poison information centers, it is a logical choice for them to provide triage services for hospitals, after hours consultation for medical practices, serve as resources for bioterrorism incidents on behalf of government and even staff medical information 'hotlines'. Each of these services has the potential to generate a significant amount of revenue. *Conclusions:* Poison information centers cannot afford to be reactive with regard to their funding. The preferred course of action is to prevent funding crises through proactive strategic planning and developing a diversified funding base.

22. How Dangerous to Human Health are Acute Dioxin Exposures in Fires?

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Introduction: Since decades dioxins are an object of study. In laboratory animals their toxicity and carcinogenicity is well known, although there are huge differences in sensitivity between various species. As a consequence of this toxicity, over the past 20–30 years several very succesful regulatory measures have been undertaken in industrialized nations to reduce dioxin exposure in the general population. However, despite many long-lasting epidemiological studies, it remains difficult to answer the question how dioxins affect human health in high exposure populations. With the exception of chloracne, hardly any consistent and statistical significant health effects have been reported in these populations. This, combined with the actual low background exposures for the general population, raises the question how dangerous nowadays acute releases of dioxins are, for instance because of fires at hazardous waste disposal sites. In the Netherlands this still causes much concern and ususally leads to rather high economic costs in trying to diminish exposure, e.g. by housing cattle and destroying the milk. With the knowledge we now have, is this concern justified? *Background Exposure:* The term dioxins refers to a large group of closely related chemicals (congeners), the polychlorinated dibenzo-para-dibenzodioxins (PCDDs) and the polychlorinated dibenzofurans (PCDFs). The most toxic representative is 2,3,7,8-tetrachlorinated dibenzo-p-dioxin (2,3,7,8-TCDD). Dioxins are formed as by-products during several chemical processes, e.g. the manufacture of polychlorinated biphenyls (PCBs) and pesticides, or during the combustion of waste. Once emitted into the environment dioxins bind to surfaces of air dust, soil, and sediment particulate matter. Dioxins are extremely stable towards physical, chemical and biological breakdown mechanisms. Because of their accumulation in adipose tissue and long halflifes dioxins enter the foodchain. Human exposure normally arises from consumption of food, especially animal fat in meat, dairy products and fish, and breast milk. The toxicity of mixtures of dioxins is expressed in toxic equivalents (TEQ) of 2,3,7,8-TCDD. In 1989, 13 municipal solid waste incinerators, at that time an important source of dioxin emission, were operational in the Netherlands, with a total dioxin emission of approximately 700 g TEQ/year. After closing several of these incinerators and improving others, the total release of dioxins in the air nowadays is less then 100 g TEQ/year. In 2001 the average exposure of the Dutch population was 1.3 pg TEQ/kg/day (the WHO TDI is 1–4 pg/kg/day). *Human Kinetics:* Absorption from the digestive tract is 50–80%, especially by the lymphatic system after the formation of chylomicrons. The distribution of 2,3,7,8-TCDD between blood and lipids elsewhere in the body is about 50–50%. In blood TCDD binds mainly to lipoproteins (80%) and proteins (15%). The main other distribution sites are liver, adipose tissue and skin. After entering the cell, dioxin binds to a protein in the aryl hydrocarbon receptor and this dioxin-protein complex enters the nucleus. Amongst other processes, this results in induction of cytochrome P-450 CYP1A1. Activation of the Ah receptor is an important first step in the toxicity of dioxin. Mainly through hydroxylation and conjugation reactions TCDD is eliminated in bile, feces and to a much lesser extent in urine. TCDD is also excreted in breast milk. The average half-life of TCDD is about 7 years. In cases of acute exposure to high concentrations the initial elimination from the blood is faster because of increased metabolism through induction of enzyms. *Clinical Manifestations:* Several long-lasting epidemiological studies have been carried out in populations with high exposures to dioxins as a result of severe accidents or use of contaminated products. However, there are only a few studies with known blood or adipose tissue levels of dioxin, e.g. the Seveso studies, and studies performed in Vietnam Veterans who handled Agent Orange. From numerous reports it is evident that chloracne can arise from exposure to dioxins. The TCDD levels in Seveso patients who developed chloracne, were above 1000 pg TCDD per gram bloodlipids. However, not all victims with high TCDD exposure and bloodconcentrations develop chloracne. Other skin lesions caused by dioxins are xerosis, follicular hyperkeratosis, conjunctivitis, Meybomian cysts, and profyria cutanea tarda. Although many other health effects are reported, only a few effects have been reported with a consistent statistic significance in the various studies. However, the clinical relevance of these effects seems insignificant. Minor increases in liver enzymes (GGT, ALT, AST) have been reported but no clinical liver disease. Even so, mild elevations in triglyceride levels, luteinizing hormone and follicle stimulating hormone and decreases in testosterone, have been reported. In a 20-year mortality study (Seveso), an overall increase in diabetes mellitus was reported, notably among women. However, the authors state that this finding should be interpreted with caution, as the diagnostic accuracy of death certificates for diabetes was poor. Evaluation of the immunological status in exposed populations has not found a relationship between exposure and impaired status. Whether or not TCDD is carcinogenic in humans remains an item of discussion. The results of long-lasting epidemiological studies are not uniform and up to now there seems to be no consistent pattern in type of cancer. There is no evidence that TCDD is responsible for a certain type of cancer in humans. Besides this, experts differ in their opinion whether a linear dose-response model or a threshold model is the most plausible model for carcinogenicity. *Dioxin Release During Fires at Hazardous Waste Disposal Sites:* In May 2000

there was a large fire at a hazardous waste disposal site in the northern part of the Netherlands. As this took place in a cattle breeding area, there was great concern about human health risks due to possibly increased levels of dioxins entering the foodchain. Several measures were taken to prevent this: housing of cattle within 5000 m, collecting all milk in a circle of 30 km, and cutting and destroying the grass within 1500 m. The National Institute of Public Health and the Environment analysed the concentrations of contaminants in smoke, grass, and milk. In air samples taken 20 m from the source, dioxin levels were 1.5 ng TEQ/m^3. This is a factor 10 above the permissible level of waste incinerators (0.1 ng TEQ/m^3). Grass samples taken 300 m from the source showed dioxin concentrations a factor 3.5 above the reference value. No milk samples showed elevated dioxin levels. *Conclusions:* The measured increased emissions of dioxins because of fires are above the actual daily permissible levels, but, compared to continuous dioxin emissions 20–30 years ago, still rather low. As health effects were not reported at these previous levels of emission, and epidemiological studies in high exposure groups reveal only chloracne as a clinical relevant consistent finding, there actually is no reason for concern about moderate short-term elevations in dioxin release. Especially with the current low background levels of dioxin, it seems highly unlikely that short-term increases in uptake of dioxins during for example fires, will result in any health effects, as this hardly contributes to the total body burden of dioxin. This applies to all age categories.

23. Effects of Dioxins on Human Health

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Background: The term dioxin represents a family of compounds. The most thoroughly studied dioxin is 2,3,7,8-tetrachloro-dibenzo-p-dioxin (TCDD). Dioxins have been associated with many human health problems. Published reports vary widely in regards to the source and the duration of dioxin exposure. Animal models have been utilized to further elucidate potential health effects. Dioxins are well absorbed by inhalation, ingestion, and dermal contact. Dioxins are widely distributed throughout the body, with the highest concentration found within the fat, the pancreas, the liver, and the skin. Dioxins bioconcentrate in humans and the main route of elimination is via the feces. *Clinical Effects:* Reports describing dioxin's clinical effects vary widely in the literature. The clinical effects associated with dioxin exposure depend on a number of factors, including the route of the exposure, the presence of other chemicals, the total dioxin body burden, the duration of dioxin exposure, the age of the person exposed, and the preexisting health of the exposed person. *General:* Anorexia, irritability, weight loss, fatigue, headache, and insomnia have all been associated with dioxin toxicity. *Gastrointestinal:* Gastrointestinal symptoms, including nausea, vomiting, abdominal pain, and gastritis may occur. Hepatitis and pancreatitis have been reported. *Cardiovascular:* Studies have suggested a link between dioxin exposure and ischemic vascular disease. *Dermatologic:* The dermatologic effects following dioxin exposure may be pronounced and have been well described. Chloracne (also known as halogen acne) is one of the most common findings in humans exposed to dioxin. Chloracne is a symmetrical dermatologic condition involving the change of undifferentiated sebaceous gland cells to keratinocytes resulting in a disappearance of sebaceous glands and the substitution of closed comedones and keratin cysts. The malar crescent of the face and retroauricular folds are the areas of the skin that are most commonly involved. The cheeks, forehead, neck, forearms, trunk, back, legs, and genitalia are also commonly afflicted. The nose, eyelids, and the auricular region are often less severely effected, except in patients with markedly elevated levels. The hands, forearms, feet, and legs are involved less. Cystic lesions containing straw colored fluid develop, especially on the face in the ''crow's feet'' area, giving a ''plucked chicken skin'' appearance. Lesions in the axilla may mimic hidradenitis suppurativa. Xerosis, alopecia, and granuloma annulare have also been reported. Hypertrichosis, primarily involving the temporal area of face and the eyebrows, occurs primarily in association with dioxin induced porphyria cutanea tarda. Punctate keratoderma, primarily involving the palms and soles, has been described and is histologically characterized by cone-shaped hyperkeratosis invaginating, but not penetrating, into the dermis. Palpebral edema and meibomian gland cysts have been reported. Hyperhidrosis of the palms and the soles may occur. Increased nail growth and nail plate thickening also have been reported. *Neuromuscular:* Dioxin causes peripheral neuropathies. Sensory neuropathies tend to be delayed in onset, persistent, and most commonly effect the legs. Polyneuropathic electromyogram abnormalities are frequently observed. The neuritis may cause limb pain of disabling severity. The motor nerves are rarely effected. Severe myalgias of the extremities, shoulders, and thorax have been reported. *Endocrine:* Hormonal alterations, including elevated luteinizing hormone and follicle stimulating hormone with lowered testosterone, have been noted in association with elevated dioxin levels. Sexual impotence has been reported as well as loss of libido (Psokitt). *Laboratory:* Numerous abnormalities in laboratory values have been reported including anemia, leukocytosis, thrombocytopenia, and decreased numbers of natural killer cells. Reports also demonstrate elevated erythrocyte sedimentation rate, C-reactive protein, fibrinogen, uroporphyrins, alkaline phosphatase, lipase, amylase, and liver transaminases

(GGT, GPT, GOT). Prolonged elevation of gamma-glutamyltransferase (GGT) has been documented in numerous reports. Dioxin induced alternations in serum lipid levels have been shown, with elevated triglycerides best characterized in the medical literature. Elevated total cholesterol and lowered HDL may also occur. *Carcinogenesis:* In regards to its potential as human carcinogen, TCDD is classified to be carcinogenic to humans (Group 1) by the International Agency for Research on Cancer (IARC). Dioxin has been associated with soft-tissue sarcoma, Hodgkin's disease, non-Hodgkin's lymphoma, gastric cancer, nasal cancer, and liver cancer in various reports. *References:* 1. Geusau A, Abraham K, Geissler K, Sator MO, Stingl G, Tschachler E. Severe 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) intoxication: clinical and laboratory effects. *Environ Health Perspect* 2001; 109(8):865–869. 2. Pelclova D, Fenclova Z, Preiss J, et al. Lipid metabolism and neuropsychological follow-up study of workers exposed to 2,3,7,8-tetrachlordibenzo-p-dioxin. *Int Arch Occup Environ Health* 2002; 75 Suppl:S60–S66. 3. Suskind RR. Chloracne, ''the hallmark of dioxin intoxication.'' *Scand J Work Environ Health* 1985; 11(3 Spec No):165–171. 4. Caputo R, Monti M, Ermacora E, et al. Cutaneous manifestations of tetrachlorodibenzo-p-dioxin in children and adolescents. Follow-up 10 years after the Seveso, Italy, accident. *J Am Acad Dermatol* 1988; 19(5 Pt 1):812–819. 5. Thomke F, Jung D, Besser R, Roder R, Konietzko J, Hopf HC. Increased risk of sensory neuropathy in workers with chloracne after exposure to 2,3,7,8-polychlorinated dioxins and furans. *Acta Neurol Scand* 1999; 100(1):1–5. 6. Michalek JE, Akhtar FZ, Arezzo JC, Garabrant DH, Albers JW. Serum dioxin and peripheral neuropathy in veterans of Operation Ranch Hand. *Neurotoxicology* 2001; 22(4):479–490. 7. Sweeney MH, Mocarelli P. Human health effects after exposure to 2,3,7,8-TCDD. *Food Addit Contam* 2000; 17(4):303–316.

24. Environmental Pollution Focus Area: Acid Mine Drainage

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There are more than 500,000 abandoned coal and metal mines in the US adversely affecting 12,000 miles of rivers and streams and more than 180,000 acres of lakes and reservoirs with acid mine drainage. This term refers to water with high concentrations of sulfuric acid draining out of surface or subsurface mines. It affects to some degree most regions in both hemispheres, and is therefore a globally distributed environmental problem. It was recently one of the issues raised in the controversial proposal to initiate gold mining in Rosia Montana, Romania. Mining activities expose gargantuan quantities of buried lithosphere materials to the oxidizing environment of the open atmosphere as the compound of commercial interest is extracted. Chemical reactions occur that compress hundreds of thousand of years of normal weathering into decades. Reactions involving sulfide-bearing mineral deposits, such as iron disulfide (FeS_2), produce sulfuric acid, which imparts a stable pH of 2.5–3 to water percolating through the fractured rock. Acid conditions subsequently mobilize metals such as aluminum, copper, cadmium zinc, manganese, and lead from rock and enable their transport in water streams draining the mine area. Naturally occurring limestone ($CaCO_3$) deposits mitigate the risk that acid rock drainage will occur in any given mining region, as oxidative weathering produces alkaline conditions. Acid mine drainage adversely impacts surface water, groundwater and riparian areas by contaminating the ecosystem with toxic metals, and altering downstream ecologies with delivery of acid. For example, fish cannot swim against an acid barrier to formerly hospitable areas and survival of salmon fry is imperiled by copper. Wild birds in a mid-western US mining area show toxic levels of lead, cadmium, and zinc, with some individuals showing clinically evident heavy metal poisoning. Chronic exposure to toxic metals in contaminated drinking or agricultural crop water poses enduring threat to localized human populations. Solubilized metals precipitate out as highly colored hydroxides when the pH is neutralized downstream. Bright orange ferric hydroxide ($Fe(OH)_3$) staining water and rocks is a reliable indicator of acid mine drainage. Neutralized precipitates can also disturb aquatic life by physically blocking the penetration of sunlight required for photosynthesis, reducing visibility for sighted animals, and reducing habitable stream bed and food for bottom dwellers. There are many strategies for control of acid mine drainage, including better assessment of risk before mining operations begin, precipitation of solubilized metals to neutralize mine effluent before discharge to the environment, passive treatment by fostering wetlands reducing environments. Acid mine drainage will affect water quality for the foreseeable future. It continues to occur at certain sites in Europe where hard-rock mines were worked by the ancient Romans. These contemporary residua of ancient activity demonstrates the potential environmental cost, literally lasting hundreds or thousand of years, which may accrue against the short-lived regional benefit of mining in areas with high risk deposits. *References:* Beyer WN, et al. Zinc and lead poisoning in wild birds in the tri-state mining district (Oklahoma, Kansas, and Missouri). *Arch Environ Contam Toxicol* 2005; 48(1):108–117. Buza M, et al. Environmental protection in the Apuseni Mountains: The role of Environmental Non-Governmental Organisations (ENGOs). *GeoJournal* 2001; 55(2–4):631–653. Jung MC, Thornton I. Environmental contamination and seasonal variation of metals

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25. Dentists and Mercury—A Toxic Cocktail?

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Elemental mercury is a liquid at room temperature, which vapourises easily. Sources include dental amalgams, and where there is spillage in dental surgeries. Preventing mercury exposure and consequent toxicity is important because therapies are controversial and of low efficacy (especially chelation therapy) and long-term clinical consequences can be very significant. Elemental mercury (Hg) is most toxic in the vapourised state. Exposure to >0.05 mg/m^3 for significant periods is unsafe (1). Inhaled vapour is absorbed, oxidises to Hg^{2+} and accumulates in brain, liver and kidneys. Exposure to high concentrations can cause acute breathlessness, fever, confusion, vomiting, tremors, polyneuropathy (2). After chronic inhalational exposure, emphysema, pneumothorax, pulmonary fibrosis and chronic neurological effects can occur (2). Dental amalgam is a major source of Hg exposure in man because Hg is the principal metal in most dental fillings (50% by weight). Whilst microleakage of mercury from amalgam has been confirmed health effects of dental amalgam have been considerably debated for years and there is no scientific consensus on any epidemiological or clinical association between amalgam Hg exposure and adverse health consequences of patients either adults or children (3–5). Some trials are ongoing (Children's Amalgam trial) (6). Some groups advocate a zero tolerance for inhaled or ingested elemental mercury and postulate dental amalgam as the aetiological factor for chronic fatigue syndrome, and Alzheimers disease (7). But what about maternal fillings and health of a developing foetus? Or, indeed a pregnant dentist? Significant levels of Hg have been measured in oral vapour, blood and in organs of animals and humans with Hg-containing dental amalgam restorations (8). In humans there was +ve correlation between I-Hg concs in liver/kidney of foetuses and number of maternal teeth with fillings (9). By implication, studies suggest significant concs of Hg may be a basis for adverse health effects but there is little definitive evidence. Thus as a precautionary measure, advice is that it may be prudent for patients to avoid, where clinically reasonable, the placement or removal of amalgam fillings during pregnancy until appropriate research data are available. What about occupational exposure of dental staff? Morton et al, 2004 showed mercury content in hair, nails and urine (mean 1.7 micromol/mol creatinine; 1 exceeded UK HSE guidance level of 20) were significantly higher in UK dentists than a socially matched population (10). Urine mercury is the most practical and sensitive marker of exposure. A cross-sectional survey of dentists in the West of Scotland and unmatched controls showed on average 4 × higher urinary mercury concs in dentists and they had different psychomotor performance, that was not correlated with mercury concs (11). Several studies have shown that chronic exposure to low concs of mercury, such as those experienced by dentists, may have an effect on psychological performance (12). It therefore makes sense that exposure to mercury vapour in dental clinics should be controlled to reduce occupational risk (7). There have been considerable reductions in exposure to mercury among the dental profession in recent years (13). In Beirut gloves and masks had the most cost-effective and significant effect on reduction of Hg concentration (14). Mercury vapour suppressant systems have been trialled in the USA (15). *References:* 1. Agency for Toxic Substances and Disease Registry ADSTR 1992. US Dept Public Health, Atlanta, Georgia. 2. Counter SA, Buchanan LH. Mercury exposure in children. A review. *Toxicol Appl Pharmacol* 2004; 198:209–230. 3. Clarkson TW. The three modern faces of mercury. *Environ Health Perspect* 2002; 110:11–23. 4. Ratcliffe HE, Swanson GM, Fischer LJ. 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26. Acute Symptoms of Cyanobacteria Toxins

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Cyanobacteria, also commonly called blue-green algae are organisms exhibiting a combination of properties found in algae and bacteria. The cyanobacteria provide a wide-ranging contribution to human affairs in everyday life with both beneficial and detrimental features. Abundant growth of cyanobacteria in water reservoirs creates problems for water suppliers. The growth of strains containing toxins is an increasingly common experience in polluted inland water systems all over the world, and also in some coastal waters. Eutrophication, the enhancement of the natural process of biological production in rivers, lakes and reservoirs caused by increases in levels of nutritiens, usually phosphorous and nitrogen compounds, can result in visible cyanobacterial or algal blooms. Cyanotoxins are usually contained within cyanobacterial cells and only rarely occur dissolved in water. Cyanotoxins belong to diverse groups of chemicals showing specific toxic mechanisms in vertebrates. Some are strong neurotoxins (anatoxin-a, anatoxin a(s), saxitoxins), others are primarily hepatotoxic (microcystins, nodularin and cylindrospemopsin), yet others (like lipopolysaccharides) appear to cause health effects (such as gastroenteritis) through mechanisms which are not yet well understood. Although experimental toxicological information clearly indicates health hazards for humans, and cyanobacteria occurrence is widespread there are only few documented cases of human illness unequivocally attributed to cyanotoxins. The symptoms attributed to cyanotoxins are not specific, the diagnosis often is not considered, until other etiologies have proved negative and the delay makes it difficult to demonstrate causal relationship to cyanobacteria and cyanotoxins. Epidemiological evidence for adverse human health effects of cyanotoxins icludes studies of human populations that have shown symptoms of poisoning attributed to presence of cyanotoxins in drinking water or other sources of water. Gastrointestinal and hepatic illness attributable to cyanobacterial toxins in water supplies have been coincident with either the breakdown of a natural cyanobacterial bloom or with the artificial lysis of a bloom leading to release of toxins from decomposing cells. In an epidemic in Brazil in 1988, some 2000 persons developed gastro-enteritis, 88 of which resulted in death (1). In Australia during a particularly extensive toxic bloom in 1981 an epidemiologic study of the local population indicated liver damage occurring simultaneously with the termination of the bloom (2). Children and persons with underlying disorders are especially in risk of cyanobacteria toxicity. In Caruaru, Brazil in 1996, water used in a dialysis centre for hemodialysis contained cyanobacterial toxins. 116 of the 130 patients hemodialysed developed symptoms and at least 50 patients died with neurological symptoms or from liver failure (3,4). Recreational exposure to cyanobacteria can cause toxic and allergic symptoms. A prospective Australian epidemiological study involving 852 subjects showed elevated incidence of diarrhoea, vomiting, flu symptoms, skin rashes, mouth ulcers, fevers, eye or ear irritations within seven days following exposure (5). Ten of 20 UK army recruits developed symptoms after swimming and canoe training in water with a tense bloom of *Microcystis spp.* Two of the recruits developed severe pneumonia (6). Paralytic shellfish poisoning (PSP) is caused by accumulation of cyanobacteria toxins, usually saxitoxins, in marine and freshwater biota, which is then consumed by humans. In addition to the type of toxin and the dose, the route of exposure to cyanobacteria toxins seems to influence probability and severity of symptoms. Ingestion of cyanobacterial toxins in concentrations high enough to cause serious toxicity is uncommon, except in cases of PSP. Inhalation exposure is one order of magnitude more toxic than gastrointestinal exposure. In our pilot-study, all persons exposed through both dermal and respiratory route had symptom, likely to be caused by Cyanobacteriae toxins inhaled with the hot steam in sauna called ''löyly'' (7). *Conclusions:* Cyanobacteria toxins can cause severe poisoning in humans under exceptional circumstances. Recreational exposure can lead to mostly vague and reversible symptoms. Definitive diagnosis of poisoning caused by cyanobacteria toxins is difficult on clinical grounds and usually requires epidemiological studies. *References:* 1. 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27. Chemical Contamination of Drinking Water Supplies—A Review of Short-Term Exposure Guideline Values

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Introduction: Public Health authorities, Poisons Centres and other health care providers are asked for advice on the health risks associated with exposure to drinking water contaminated by a variety of naturally occurring and man-made chemicals. The contamination may be chronic or short-term. Decisions on the safety of a water supply and appropriate risk management action may be required promptly and may have a significant impact on a large population. Sound advice, based on toxicologically robust evidence, is therefore essential to enable interventions which are proportionate to the health risk. Ideally, chemical contaminant guideline values should help ensure that actions do not result in the unjustified disruption of domestic water supplies, whilst also protecting public health where a significant risk does exist. Existing chemical guideline values, which are routinely available, are often determined using models based on life-time consumption. These may be inappropriate for use in conducting a risk assessment in a short-term, acute exposure chemical contamination incident. Action based on such values might therefore be unnecessarily precautionary, resulting in avoidable interruptions to water supplies. A survey was conducted to determine the availability, and the toxicological and methodical bases for deriving guideline values for chemical contaminants in drinking water and to assess their suitability for use in acute, short-term exposure incidents. *Methods:* Chemical contaminant guideline values available either publicly or commercially in the UK, USA and elsewhere, were reviewed. The origins, derivation and toxicological basis for each set were analysed. The appropriateness for use in acute, short-term chemical contamination incidents was examined on the basis of the toxicological risk characterisation. For comparison, the methodology used to derive acute exposure guideline values for airborne chemical contaminants in the US was also reviewed. *Results:* Five sets of guideline values for chemicals in drinking water were identified: WHO Guidelines on Drinking Water Quality; Suggested No Adverse Response Levels (US and UK); Health Advisories (US); and Significant Medical Risk Values (Scotland). WHO guideline values for drinking water are now in their third edition (2004). These include health-based guideline values intended to represent the concentration of substances, excluding carcinogens, that should not result in any significant risk to health over a life-time consumption. These are derived from peer reviews of published literature on both toxicological assessments and epidemiological evidence. Some guideline values are relevant in acute exposure situations but relatively few are explicitly designated as such. Suggested No Adverse Response Levels (SNARLS) were published by the US National Academy of Sciences in ''Drinking Water and Health'' between 1977 and 1989. These were explicitly derived to represent the concentration of a substance considered to present no significant health risk over 24 hours or seven days. These values were based on a NOAEL or LOAEL with appropriate safety factors. These values were derived only where human data or sub-lethal animal data was available and have not been updated. The US EPA have published as Health Advisories (HAs) starting in 1987, now covering some 175 chemicals. HAs are derived for short-term exposures (1 day or less, or 10 days or less) long-term (7 years or less) and life-time exposures to drinking water. Non-carcinogenic hazards are assessed and NOAEL or LOAEL are combined with appropriate safety factors depending on the time frame of exposure. More recent HAs have also considered organoleptic properties of chemicals where these might give rise to detectable nuisances rather than explicit health effects. UK SNARL values are a set of guidelines produced by NCET—WRc/NSF in England and are available on a commercial subscription basis. These values are also derived from either existing peer reviewed scientific data or, where absent, by in-house toxicologists using standard toxicological techniques to determine a NOAEL or LOAEL value to which safety factors are then applied. Significant Medical Risk Values (SMRVs) were produced in Scotland prior to 1996. Values were derived largely based on other published guidelines, particularly WHO guidelines and adjusted to reflect an acute exposure scenario rather than a lifetime exposure. These levels were not in themselves designed to be used as safe exposure limits but were intended to set a threshold to indicate when discussion was needed between water providers and local Public Health authorities, to determine if a health risk existed. This review found that the existing guidelines rely on standard toxicological principles, based on the nature of the health effects. Cancer and non-cancer outcomes are generally treated differently. Cancer is regarded as a probabilistic event with no actual threshold limit value, below which there is zero risk. Non-cancer health outcomes are generally regarded as threshold related events, which may be completely preventable, if exposure is maintained below a defined ''no-effect'' concentration value. The main limitation in deriving robust guideline values is the availability of suitable evidence that is commensurate with both the critical effects and duration of exposure. Good quality epidemiological evidence is often not available. Reliance often has to be placed on the extrapolation of data derived from animal experiments. Multiple uncertainty factors then have to be incorporated to provide a sufficiently wide extra safety margin. Such methodologies are therefore likely to result in conservative estimates for safe exposure thresholds. Some differences exist between the methods used for deriving water exposure guidelines and those for airborne exposures. The volume of water consumed is the main determinant of waterborne cumulative exposure, whereas for air, the

duration of exposure is relatively more important. Some short-term water guidelines do take explicit account of exposure duration as well as the volume of water consumed, e.g. the US EPA Health Advisories and the UK SNARL values. For drinking water, the exposure is potentially discretionary, in that individuals have a degree of choice as to which water they drink. For airborne chemical hazards, there is little if any choice for the individual in the air to which they are exposed. As a consequence, although the basic toxicological principles employed are similar, there is a higher degree of sophistication in the methods used to derive ranges of safety values, as found in the US AEGLs programme. *Conclusions:* A variety of guideline values for chemical contaminants in drinking water exist. Some are designed specifically for use in short-term acute exposure scenarios. There is variation between the values for the same chemical in different guidelines, attributable in part to the variation in the toxicological safety factors. There is no single agreed set of guideline values for short-term exposures available for use by public health authorities and poison centres. This creates difficulty in providing soundly based and defensible advice when asked to comment on the health risks associated with an acute chemical exposure incident affecting domestic water supplies. In the absence of agreed definitive guidance, use of the most precautionary levels, which may themselves be over-protective, would seem prudent. There would be considerable advantage in having a single set of definitive short-term exposure guidelines to complement the widely accepted life-time exposure standards already set by WHO. A first step to attaining such a set of guideline values would be to agree on criteria for use as standards against which existing and any proposed values could be compared.

28. Neurological Disorder and Burden of Organochlorines in a Population Living on a Bombed Depot for Locust Control in Hargeisa/Somaliland—A Controlled Study

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Introduction: The capital of Somaliland Hargeisa was bombed by air raids during a civil war. A depot for locust control was destroyed and 80,000 litres of pesticides contaminated the soil. A population of returners were resettled close to this depot. Concern arose about the hazard for this population because the soil they were living on was found to be highly contaminated with organophosphorus (OPCs)—and organochlorines compounds (OCCs). The administration of Somaliland called a WHO party to examine this population. *Methods:* A group of 59 persons living on this soil (verum) was compared to a group of 60 persons living at the other side of Hargeisa (control). All persons underwent an interview about their habitation (not reported here) and a thorough neurological examination. The neurological examination was summarized in a neurological score (0–30) points with the emphasis on signs of polyneuropathy. A score above 20 suggested polyneuropathy. Urine and blood was taken for analytic assessment of residues of OPCs and OCCs. Also studied were residues of OPCs in the urine. Alpha-, Beta-, Gamma-HCH, heptachlor, dieldrin, ppDDT and DDE were quantitatively measured in the serum. *Result:* The sum neurological score in the verum group was 7±4,76 in the control group to 10,69±7,02. There were two persons with a score above 20 in the verum group and 5 in contol group. The laboratory results of the OCCs are given in Table 1. Less than 10% of all test persons showed positive results for OPCs residues. Alpha-HCH was not detected in any sample. Mean value for all the other OCCs and the

TABLE 1

	β-HCH above detection limit	γ-lindane above detection limit	Heptachlor above detection limit	Dieldrin above detection limit	ppDDT above detection limit	DDE above detection limit
Verum	18/59	1/59	59/59	1/59	51/59	59/59
Control	26/60	14/60	60/60	3/60	52/60	60/60
Mean value (μg/l)						
Verum	0,623	(0,15) n=1	0,765	(0,32) n=1	1,365	2,448
Control	0,884	0,22	0,874	(0,54) n=3	2,588	6,563

amount of persons tested positively were higher in the verum group. Heptachlor was found in everybody. DDE was significantly higher in the verum group. *Conclusion:* Persons living close to a bombed locust control depot have lower OCC burden than the control, amazingly. This corresponds to the neurological examination as a control group living further away shows higher incidence of neurological pathology. The reason for the higher DDE in the control group may be due to the contamination of the whole area and the longer time of exposition.

29. Mass Tropane Alkaloid Poisoning Due to Buckwheat Flour Contamination

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Objective: We performed a risk assessment of buckwheat flour accidentally contaminated with Datura alkaloids. In order to estimate the exposure we attempted to establish the doses of atropine and scopolamine ingested by the poisoned consumers. *Case Series:* Buckwheat flour is commonly used in preparation of traditional dishes in Slovenia. In September 2003, cases of domestic food poisoning with a typical syndrome of tropane alkaloid toxicity: dry mouth, hot red skin, blurred vision, tachycardia, urinary retention, ataxia, speech disturbance, disorientation and visual hallucinations, were identified. All victims reported ingestion of a traditional dish made of buckwheat flour a few hours prior to the onset of symptoms. The severity of poisoning in the identified cases ranged from mild to moderate. Symptoms had ceased spontaneously within 48 hours. Qualitative analyses using GC-MS confirmed the presence of atropine and scopolamine in four samples of buckwheat flour. Examination of whole buckwheat grain showed up to 190 *Datura stramonium* seeds/kg of grain. We established an ad hoc telephone self reporting scheme which identified 73 cases with classical symptoms of tropane alkaloid toxicity associated with the use of buckwheat flour. A questionnaire was sent to all the consumers who had reported symptoms to refine the strength of association between the exposure and effects and to establish the ingested doses. In all 64 consumers who returned the questionnaire we were able to establish a link between buckwheat flour consumption and developing of a typical syndrome. The qualitative analyses of buckwheat flour using LC-MS/MS showed levels of atropine and/or scopolamine above the limit of quantification, 3 μg/kg, (limit of detection 1 μg/kg) in 20 of 43 samples. The highest levels of both alkaloids were found in the flour consumed by a family of eight: 26 mg of atropine/kg and 12 mg scopolamine/kg. The members of this family consumed between 53–137.6 μg of atropine/kg body weight and between 24.5–63.5 μg of scopolamine/kg of body weight. These doses are well within the toxic range reported in the literature. All buckwheat flour and buckwheat flour products had been recalled. Legislation on grain purity and buckwheat flour was amended on the grounds of our risk assessment. No further cases of poisoning were reported. *Conclusion:* A mass poisoning due to accidental contamination of buckwheat flour with Datura alkaloids, atropine and scopolamine, occurred in Slovenia with no long term sequelae. The incident could have been avoided had appropriate milling practices been used. As a result of this incident risk assessment was performed and national food legislation amended to prevent further poisonings.

30. Prospective Study on the Effects of Sodium Percarbonate Containing Fabric Cleaners

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Objective: In recent years a new product group has been added to the available assortment of fabric cleaners in the form of sodiumpercarbonate (SPC) containing powders. After dissolving SPC (100% w/w) in water, sodiumcarbonate (68% w/w) is formed as well as hydrogenperoxide (H_2O_2, 32% w/w) as the stain removing agent. Most reports of exposures to H_2O_2 state that concentrations below 10% are usually not harmful in small amounts. Based on the amount of H_2O_2 theoretically released by SPC, significant local and systemic effects could occur. However, no reports on human health effects of SPC were found. The Dutch Poisons Information Centre (DPIC) conducted a prospective study to compare the effects of exposure to H_2O_2 containing products to those containing SPC. *Methods:* From 18-05-2003 we gathered follow-up data on all reports to the DPIC concerning exposure to SPC and H_2O_2 containing products. *Results:* Out of 92 cases reported (until 15-11-2004; study is being continued) we received follow-up information in 64 cases; 49 children from 1–10 years of age (average 2.5

TABLE 1

	H_2O_2	SPC powder	SPC dissolved
Total exposures	31	16	17
No symptoms	19 (61%)	14 (87%)	10 (59%)
Symptoms	12 (39%)	2 (13%)	7 (41%)
Reported symptoms	Vomiting (5)	Vomiting (1)	Vomiting (1)
	Nausea (4)		Nausea (3)
	Sore throat (1)		Sore throat (4)
	Coughing (3)		Coughing (1)
	Endoscopic: minor oesophageal erosions (1)	Abdominal distention and burping (1)	Oesophagitis requiring drip-feed (1)
	Diarrhea (1)		

years) and 15 adults. The exposures involved a liquid containing H_2O_2 (around 10%) in 31 cases, dry SPC (max. 80%) containing product in 16 cases and a homemade solution of SPC in water (variable concentrations, around 10% according to user instructions) in 17 cases. Reported symptoms are detailed in Table 1. Accidental exposure to H_2O_2-solutions with concentrations around 10% and dissolved SPC powder caused mainly local irritation of the mucosa and mild abdominal discomfort. Dry SPC powder ingestion caused less local effects than dissolved SPC. Marked gas formation inside the GI-tract with burping and abdominal distension was observed in one case after ingestion of approximately 15 grams of dry powder (80% SPC) by a 3.5 year old boy, weighing 22 kg (approximately 0.5 g/kg SPC). No signs of systemic absorption or formation of gasembolism in the bloodstream were observed in any of the groups. *Conclusion:* Considering the amount of H_2O_2 that can be released from SPC, the observed local effects after SPC exposure were remarkably mild in our series. No systemic effects were observed. We have no clear explanation for this unexpected finding and further investigation of the SPC induced health effects is needed.

31. Reduced Level of Consciousness in the Emergency Room—Characteristics of Poisoning vs. Other Underlying Causes

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Objective: Unconsciousness is a diagnostic challenge in the emergency room. Systematic studies on underlying aetiologies, characteristics and prognosis are scanty. We present a preliminary report of an ongoing prospective observational study. *Methods:* Adults admitted to the nontraumatic emergency room at either the Karolinska Hospital or the South Hospital in Stockholm between Feb 2003 and April 2004 with a Glasgow Coma Scale score <11 were included. The GCS score was entered into a study protocol which was completed with data from the medical record within one month. *Results:* 415 patients were included. Poisoning caused the unconsciousness in 163 cases (39%). The other underlying causes were focal coma (i.e. stroke) in 24%, epilepsy in 13%, miscellaneous metabolic disturbances in 20%, psychogenic coma in 1% and unclear aetiology in 3%. Toxic agents were ethanol alone in 68 of the 163 poisonings, ethanol and hypnotics/neuroleptics in 31, hypnotics/neuroleptics in 33, heavy narcotics in 13, and miscellaneous toxicants in the remaining 18. Flumazenil was administrated to 61 poisoned patients, 54% of whom responded, and naloxone was given in 36 cases of poisoning, 36% of whom responded. There were no complications related to antidote treatment. Acute CT-scan of the brain was performed in 26 of the 163 poisonings, all but one with a normal result. Table 1 shows a comparison of GCS score, age and outcome in the two study groups. The six fatal cases of poisoning were all associated with complications already present on admission. *Conclusion:* Overall, poisoning was the most common cause of nontraumatic coma. Among patients below the age of 40, impaired consciousness was caused by poisoning in 84%. By contrast, in patients over 60, poisoning was the cause in only 11%. The average GCS score on admission was identical in the two groups, consequently the level of unconsciousness was not useful in distinguishing between poisoning and other aetiologies. The frequent use of flumazenil and CT-scans was surprising, and may reflect major diagnostic difficulties and/or liberal use.

TABLE 1
GCS* score, age and outcome in 415 consecutive cases of nontraumatic coma

	Non poisoning (n=252)	Poisoning (n=163)
Mean GCS score on admission	6	6
Mean age	69 years	43 years
Age <40 years (n=94)	15 patients (16%)	79 patients (84%)
Age >60 years (n=200)	177 patients (89%)	23 patients (11%)
Sequelae at discharge	40 patients (16%)	1 patient (0.6%)
Fatal outcome	89 patients (35%)	6 patients (3.7%)

*Glasgow Coma Scale (3–15); 3=deep coma, 15=fully awake.

32. TOXBASE: A UK Internet Poisons Information System—The First Five Years

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Introduction: The UK National Poisons Information Service (NPIS) was established in 1963, and has provided information for medical professionals (not for members of the public) by telephone since that time through its regional centres. In 1983 an on-line information database was developed to make information available to remote terminals using Viewdata technology. This demonstrated the potential of this approach to poisons information, and over the next 16 years 600 users were registered to the system. In 1999, following a government review of the NPIS, a strategic decision was made to move towards internet provision as the primary means of poisons information delivery in the UK. This was in the face of increasing telephone call loads, and a restricted budget. TOXBASE became available on the internet in September 1999. It is available free to UK NHS service users, and at an annual charge to overseas users and commercial companies. Users are normally hospital departments, but may be general practitioners, laboratories or public health units. In the past five years the registered user base has increased approximately 8-fold to 4700. In 2004 there were 384,550 logons to the system, accessing over 770,000 product monographs. 60% of the accesses were from accident and emergency departments. In 1998 the UK health department instituted a 24 hour public health information telephone line system, NHS Direct. TOXBASE is provided to this service as an integral component of its activities, and as a result 29% of TOXBASE use in 2004 was from NHS Direct and its sister Scottish service. Other hospital departments including laboratory, intensive care units, and pharmacy, contributed 8% of the database usage. Primary care physicians and others accounted for the remainder. *System Details:* TOXBASE contains up to 12,000 monographs, which are updated from one centre of the NPIS (Edinburgh). Since the move to the internet a uniform structure of database content, monograph review, and professional advice, has been developed by the Directors (clinical consultants) involved in the service, collaborating with the TOXBASE editorial group in Edinburgh, and all entries onto TOXBASE are now reviewed by the NPIS as a whole. The information is held on an Access database, hosted on a commercial server, with a secondary backup site in case of primary site failure. The site is updated daily, but in an emergency alerts can be placed within 2–3 hours. *The Database:* The database currently holds around 12,000 product monographs, many of which are linked to approximately 200 general features and treatment sections. These may be about a drug, e.g. paracetamol, a class chemical, e.g. carbamates, or other household products, e.g. detergents. As many commercial, particularly household, products are similar the database includes general entries for common product types, such as washing up liquid. The database management and review is a key task, and one of increasing complexity. TOXBASE currently has a 3–5 year rolling review, but more effort is placed on those products accessed frequently than those accessed rarely. Each year the top 100 accesses are noted, and the entries in all these products subject to specific review. In the UK 10.6% of product accesses for 2004 were for paracetamol. The top 10 agents accounted for 18% of the product enquiries, and the top 100 47%. Numbers then decrease exponentially. Over the past five years there has been relative stability about the most common compounds being accessed, and the top 10 include paracetamol, ibuprofen, ethanol, diazepam, aspirin, caffeine (as a component of analgesic combination tablets), codeine (principally co-codamol) and zopiclone. The database can be used to track changes in poisons enquiries, such as may follow a significant license change to a marketed

pharmaceutical. In recent years ecstasy, previously a top 10 compound, has dropped out, but venlafaxine and citalopram have had increasing enquiries. In addition to providing treatment monographs, TOXBASE includes a range of other information relevant to poisons management. Information held includes, for example, antidote availability; a series of specially prepared monographs written for emergency physicians, public health physicians and for provision to members of the general public in case of deliberate release of chemicals and biologicals; full details of laboratory services in the UK offering special assays; specific teratology information (authored by the National Teratology Information Service) currently containing 125 monographs on chemicals, drugs and other substances commonly encountered in pregnancy. A series of monographs on the management of common conditions in pregnancy, almost exclusively used by pharmacy and medicines information departments is available. These monographs were accessed in excess of 33,000 times in 2004. Feedback from enquirers is encouraged on the database. Forms are available for clinical data to be entered, specifically about new drugs and new products, and it is also possible to tag individual entries in order that all accesses are monitored in real time. This process is currently being used for a UK survey on pesticide exposures. In order to ensure TOXBASE is used optimally by health staff an educational programme has been developed, and a web based package is currently being written based on paper data currently in use. This will support a range of clinical staff, including nurses and environmental officers working for public health departments, to optimise their use of the database. *Summary:* in the past five years telephone call loads to the NPIS have reduced significantly. Numbers of consultant referrals have, in contrast, not fallen—indicating the database has not prevented the telephone enquiries regarding more serious cases of poisoning reaching the NPIS. The ability to provide standardised information across the whole of the country's health services with relatively low cost illustrates the potential for internet services to be used to support, but not replace, poisons information telephone services. The possibility of integrating these services with public health access telephone services has been illustrated, and the potential for these services to free expert poisons information scientist time for more strategic work is a further benefit. The days when the number of telephone calls a centre receives is seen as an indication of effectiveness are numbered.

33. TOXINZ: Internet Poisons Information Database

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Introduction: The New Zealand National Poisons Centre has developed TOXINZ (www.toxinz.com), a poisons information database containing detailed recommendations regarding the medical management of the poisoned patient. In January 2005 this resource covered some 87,000 chemicals and trade products, pharmaceuticals, plants, and hazardous creatures: with medical management recommendations reviewed by an international editorial board. Whilst currently an Australasian based product it is provided free to Poisons Information Centres (PICs) around the world on request. It is considered that the innovative information technology now driving TOXINZ has significant potential to provide a truly international poisons information resource. *Background:* The New Zealand National Poisons Centre was created in 1964 and since that time it has collected and collated hazard information, and produced treatment recommendations. This information was then provided to both health professionals and the lay public via telephone. After 30 years of delivering advice in this way it was realised that the significant advances in information technology and communications introduced during this period had not been applied to the PIC service. In an effort to improve efficiency and supplement existing telephonic communications, work was undertaken to adopt these technologies and develop a new model of service provision centred on the electronic distribution of information. As a consequence the existing database software was replaced with a ''relational'' application achieving an estimated order of magnitude of increased efficiency in information management. This project was complete in 1998 and the information distributed on CD-Rom to select hospital emergency departments for critique. Interest from users was intense, and from 2000 the CD-Rom was more widely distributed on a subscription basis with six monthly updates. However, this approach was found to suffer a number of drawbacks including: significant production and distribution costs; delay in provision of updates; reduced toxicovigilance capability; use of CD-Rom data beyond expiry; and unauthorised reproduction and distribution. To remedy these concerns, the database software was further upgraded to provide Internet access, and the CD-Rom removed from circulation. This new web-based poisons information resource was named TOXINZ. It allowed weekly information updates, cost less to distribute, was more secure, and provided an ability to monitor information access. After the first year of release a survey was conducted of subscribing emergency departments confirming a high rate of use and satisfaction (1). A second survey conducted two years later in 2003 identified increased utilisation of TOXINZ, and more accurately defined real-world limitations of the application of web technology in the emergency department setting. Assessment of these limitations indicated a fundamental difficulty in projecting clinical information and decision making tools to the patient's bedside. During this period TOXINZ was also made available free of charge to any PIC who applied. By the end of 2004 Centres were utilising TOXINZ in: Australia, Malaysia, South Africa,

Vietnam, Trinidad and Tobago, Russia, Japan, and Singapore. This international use led to recognition that countries had unique poisons information needs. Examples included requirement for local chemical product and pharmaceutical trade names; local flora and fauna identification; diverse management approaches; and an ability to identify local resources such as specialist treatment facilities or advisors. This interaction also highlighted the potential usefulness of the provision to participating PICs of a mechanism by which contributions of local content could be made to the database for the mutual benefit of all those utilising the resource. However, such contributions required a mechanism for data input and review, and would increase the rate of expansion of TOXINZ leading to difficulties in the effective management of database content. Even though the ''relational'' approach had provided huge efficiencies, a new methodology would be required to allow both continued growth, and an ability to ensure management recommendations reflected current standards of care. With such issues in mind the software behind TOXINZ was again redeveloped and a revolutionary data management concept introduced which allowed another leap in efficiency. In January 2005 the new database engine was introduced. *Discussion:* This innovative database system has the ability to accept information via the Internet: and it is hoped the free access scheme will encourage participating PICs to add details of products, plants and hazardous creatures from their region to existing management recommendations. While the medical management information is currently primarily maintained by the New Zealand National Poisons Centre, contributions can be accepted from any PIC participating in the TOXINZ project. These recommendations are then reviewed by an international editorial board and, once accepted, immediately made available to users. Membership of the board is by invitation and follows recognition of outstanding contribution to clinical toxicology and/or toxinology. Editors are requested to review areas where they possess acknowledged expertise, and receive payment to ensure the highest standards are maintained. Further functionality has been included to allow development of geographically specific websites to project management options most suited to a particular global region. Given the difficulties identified in delivery of clinical information to the point of care TOXINZ is also exploring approaches to increase accessibility to quality poisons information in settings outside of the PIC environment. These include allowing other medical software applications direct access to data, thus seamlessly projecting reliable poisons information directly to a clinician's patient management application: and developing a version for use in hand-held devices with wireless Internet connectivity. *Conclusion:* The TOXINZ poisons information database is applying advances in information and communications technologies to gather, review and project robust and current poisons management recommendations. This resource is provided free to any PIC, in the hope that such Centres will appreciate the benefits of contributing regional poisons information for the advantage of all users. *Reference:* 1. Watts W, Fountain J, Reith DM, Herbison P. Clinical utility of an electronic poisons information and clinical decision support tool. *Int J Med Info* 2003; 71:3–8.

34. The World Library of Toxicology and Other Online Tools from the US National Library of Medicine

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More than ever, toxicologists must maneuver in a global environment. As developing countries adapt the habits of Western nations, there is an increase in the potential for environmental contamination by hazardous substances, which honor no national borders. The World Library of Toxicology, Chemical Safety, and Environmental Health is a portal to resources—governmental, non-government, and academic—in toxicology, on a country-by-country basis, and including information on multi-national and international organizations. This multilingual tool is a means of presenting toxicological activities taking place throughout the world, with the potential of enhancing communication, minimizing duplication of effort, and stimulating collaboration. This presentation will offer an overview of the rationale and features of the World Library, created by the U.S. National Library of Medicine's (NLM) Toxicology and Environmental Health Information Program. In addition, it will provide an opportunity to summarize related NLM-produced information activities and databases relevant to the clinical toxicology community.

35. The Role of Poison Centers in Public Health Response and Toxicosurveillance

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Background: In 1953, a pediatrician in Chicago, Illinois opened the first United States (US) Poison Center (PC). Over the years, centers grew in a patch work manner across the US. At one point, there were 500–600 so called PCs in the US. Many were simply telephones in hospital emergency departments or pharmacies with little or no defined structure; no standardized data

collection system and limited staff training. Today through the work of hundreds of dedicated individuals and the American Association of Poison Control Centers (AAPCC) there are 61 centers in the US. These Centers have a standardized, computerized data collection system, a nationwide toll free phone number, and toxicology training for poison specialists and physicians. The data gathering, regulatory and reporting functions of regional poison centers vary from State to State. PC data collection methods and interpretation continue to evolve nationally at the AAPCC and regionally at individual PCs. *Objective:* Characterize the role of national and regional PC toxicosurveillance data for public health event response. *Methods:* Traditionally PC data was reported via annual or quarterly reports. These retrospective reports typically go to funding agencies, state and local health departments and governmental agencies. Development and implementation of near real-time toxicosurveillance heralds a major change in how PC data is used and valued. Data from 61 centers is uploaded to the AAPCC in Washington DC every twenty minutes where daily and intra daily analysis takes place. Data analysis focuses on statistical evaluation of case volume, clinical effects, specific toxins, and syndrome definitions. Regional PCs receive ''outlier'' signals each day. These alerts are then evaluated and validated on a regional and local basis. *Discussion:* Poison center data serves many roles in the public health arena. Our national database provides a wide range of information on case volume, clinical effects, and exposures. Data can be used to identify events of public health significance. Toxicosurveillance augments public health infrastructure for prevention and early event detection. Rapid identification of outbreaks/clusters facilitates implementation and evaluation of prevention and control measures, epidemiologic studies, identification of emerging hazards, and research. With world events, collection and analysis of these data has reached a new level of importance. PC toxicosurveillance at a national and regional level offers the opportunity for early detection of toxin related events of public health significance. Toxicosurveillance effort requires the combined efforts of PCs and public health agencies. Surveillance data analysis by individual PCs can be utilized to validate national surveillance outliers and provide detailed supplemental information on a local basis not available by national analysis alone. Data must be shared and analyzed nationally and locally. While national surveillance can detect outliers, local poison centers have specialized knowledge of regional characteristics and investigative abilities not available at the national level. *Conclusion:* Data collection and toxicosurveillance are core competencies of PCs. These capabilities are an integral part of the public health system enhancing infrastructure and surveillance activities. PC toxicosurveillance signals monitored nationally and validated locally can identify sentinel events of public health significance.

36. The EAPCCT Website and the European Poisons Centres Network

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Objective: The internet provides a powerful, fast and efficient tool to create networks locally and globally. Important intentions of the EAPCCT as outlined in art. 2 of its constitution are to ''unite into one group individuals whose professional activities are concerned with clinical toxicology whether in a poisons centre, university, hospital or in government or industry,'' to ''facilitate the collection, exchange and dissemination of relevant information among individual members, poisons centres and organisations interested in clinical toxicology,'' and to ''establish and maintain effective collaboration with governments, governmental organisations, professional bodies and other groups or individuals concerned with clinical toxicology,'' goals which can be achieved by the means of the association's website. The goal of this analysis is to determine how the association's website can contribute to its aims, and to investigate to what extent the European PCs are using internet technologies today as compared to the 2000 survey. *Methods:* Literature searching using ''Poison Centres,'' ''Network,'' ''Toxicovigilance,'' and ''Preparedness'' as search terms, analysis of EAPCCT documents. *Results:* The EAPCCT Poison Centre directory lists 79 PCs in 33 countries, of which 71 (90%) have e-mail access and 36 (46%) have an own website. In the year 2000 Poison Centre survey performed by the EAPCCT, 48 of the 60 PCs responding indicated to have e-mail (80%) and 24 to have an own website (40%). Data exchange between PCs may successfully detect toxic risks. A most recent example is the 2001–2002 outbreak of respiratory disease after use of waterproofing spray which had been detected first by national Poison Centres. An e-mail survey using the EAPCCT member directory revealed within a few days that the Netherlands and Switzerland were concerned but not other countries. International data pooling between Poisons Centres is virtually absent in Europe. First steps are taken by the German speaking Poisons Centres in Germany, Austria and Switzerland starting collecting and pooling data on fatal cases. *Conclusions:* Poisons Centres are well established in the European countries, and increasingly use internet technologies. In the view of globalisation of the use of chemicals and toxic products, and facing biological and chemical terror threats, the intrernational collaboration of Poisons Centres needs to be

more efficient in the future. As Poisons Centres are frequently the first to be addressed to because of a sudden increase of toxic symptoms or unexplained effects after exposure to chemical substances, they are able to play a key role in national and international toxicosurveillance. Like single Poisons Centres on a national level, an international network of Poisons Centres is needed to alert the international community early about emerging chemical risks. Multiple techniques can be used: E-mail surveys which are successfully performed today, are low-cost and very efficient, but depend on the initiative of single individuals. A password-protected member's forum can serve to collect important observations from single Poisons Centres but, for toxicovigilance purposes, the incoming information needs to be screened and evaluated by the webmaster continuously. In the future automated data-mining in a pooled database using syndromic surveillance would enable real-time toxicovigilance, but is very expensive and depends on data harmonization of the participating European PCs. Regional data collection with central reporting comparable to the adverse drug reaction reporting system would be needed. The EAPCCT website could well serve as a platform for this purpose, to play its proper role in the national and international public health surveillance, alert and response systems. *References:* 1. Public Health Preparedness and Response to Chemical Incidents in Europe. WHO, Geneva 2002. 2. OECD Guiding Principles for Chemical Accident Prevention, Preparedness, and Response. 2nd ed. OECD, Paris 2003. 3. Public Health Response to Biological and Chemical Weapons. 2nd ed. WHO, Geneva 2004. 4. Public Health and Chemical Incidents. WHO, Cardiff 1999. 5. Bowen HJ, et al. Community exposures to chemical incidents: development and evaluation of the first environmental public health surveillance system in Europe. *J Epidemiol Community Health* 2000; 54:870–873. 6. Kupferschmidt H. Epidemy of acute respiratory illness linked to use of waterproofing textile and leather spray. *J Toxicol Clin Toxicol* 2003; 41:665–666. 7. de Groot R, et al. Sudden increase of acute respiratory illness after using a spray product to waterproof clothing and shoes. *J Toxicol Clin Toxicol* 2004; 42:443. 8. Syndromic surveillance *MMWR* 2004; 53 (suppl):1–264. 9. Foldy S, et al. Syndromic surveillance using regional emergency medicine internet. *Ann Emerg Med* 2004; 44:242–246.

37. Future Potential of Poisons Information Systems for Global Surveillance

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Introduction: Poisons information (control) centres have developed over the past 50 years from merely providing information to collecting and analysing it. In recent years increasing interest has focussed on the potential for poisons information systems to become more closely associated with development of public health policy in respect to both surveillance, and more specifically alerting, to new patterns in poisoning. Their potential for use in an alerting network in the event of deliberate (terrorist) release is a key issue. Up until now the majority of countries in Europe have developed poisons services largely independent of each other. The European Association has promoted some common approaches, for example the poisoning severity score (Persson et al, 1998), but to a large extent most European countries have their own method and extent of data collection and analysis. The WHO, through the IPCS and other agencies, has developed the specific categorisation systems for drugs and chemicals, but these are not being universally adopted within the wider poisons network. To maximise their public health benefit and improve timely dissemination of specific alerts, poisons services need not only to serve their own localities and/or countries, but should also have an eye on the wider world population. Only in this way will multi-country surveillance and alerting be possible. *Discussion:* When considering data collection necessary for alerting and surveillance it is necessary to consider the uses to which the data will be put. Evaluation of the effectiveness of surveillance will depend on common approaches to data collection and analysis. Function will affect the manner in which data is collected and handled as well as the required frequency of analysis. Key variables need to be identified, and may vary from symptoms, recognised syndromic patterns (e.g. nerve agents), specific circumstances of exposure, or enquiries regarding specific (new) products or ingredients. Potential uses of poisons information centres surveillance include detecting of covert releases in case of terrorist attacks, and, in every day life, public health safety programmes (targeted at monitoring toxicity from marketed products, drugs or chemicals). Also, more specific data collection systems can be utilised to establish better dose-effect relationships and treatment, and assess the effectiveness of advice given, in order to improve the processes of poisons information provision. This is potentially extremely valuable for less common poisonings. In order to achieve these objectives poisons services need to consider unification of approach to data collection. A national data collection system like TESS in the USA will not be easily achievable in Europe, but new imaginative approaches to existing collection, exchange and analysis of poisons data is an exciting challenge for the near future. *Conclusion:* The first steps in this process are made by bringing European countries together to participate, through the EAPCCT, in the

development of an European Community health surveillance and alerting system. *Reference:* Persson HE, et al. Poisoning severity score. Grading of acute poisoning. *J Toxicol Clin Toxicol* 1998; 36(3):205–213.

38. Formate Analysis as a Diagnostic Tool in Methanol Poisoning

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Objective: Early diagnosis is essential for successful treatment of patients poisoned with methanol. Detection of methanol usually requires a gas chromatographic method, not available in most hospitals. Methanol poisoning may also be suspected indirectly by calculation of the osmolal and anion gap, since methanol increases the osmolal gap in serum and its metabolite formate increases the anion gap. The sensitivity of these indirect methods is not good at low concentrations of methanol or formate. We studied the usefulness of formate measurement in diagnosing methanol poisoning. *Methods:* Serum formate was measured enzymatically in 15 patients during a large outbreak. Formate was measured enzymatically on a Cobas Mira analyzer using formate dehydrogenase and nicotinamid adenine dinucleotid (NAD). Day-to-day coefficient of variation was 5%, and the upper reference limit was 1.8 mg/dL (0.4 mmol/L). *Results:* Methanol was detected in all 15 patients of whom 14 had serum formate concentrations above the reference range. Anion gap was increased in 11 of 11, and osmolal gap in 11 patients of 15 examined. Metabolic acidosis was present in 12 of 15 patients, but pH was below 7.30 in only 9 of them. Four patients with no symptoms had formate concentrations in the range 2.3–38.2 mg/dL (0.5–8.3 mmol/L), indicating that increased serum formate is a sensitive indicator of methanol poisoning. *Conclusion:* Our results proved formate analysis to be a simple, sensitive and specific way of diagnosing methanol poisoning. Confounders are patients admitted early with concomitant ethanol ingestion and therefore no acidosis. This problem may, however, be overcome by repeated formate analysis in patients developing metabolic acidosis.

39. Prognostic Features in Methanol Poisoning: Role of Respiratory Compensation of Metabolic Acidosis

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Objective: In methanol poisoning, the patient's ability to compensate the metabolic acidosis by hyperventilation has been suggested as a predictor for better outcome. *Methods:* In September 2001, 147 patients were admitted to Pärnu Hospital in Estonia over a few days. Of these, 111 were confirmed poisoned by methanol. Serum pH and pCO_2 upon admission were compared between the patients who survived and those who died. *Results:* As expected, survivors as a group showed a decreasing pCO_2 with decreasing pH, indicating ability to compensate for the metabolic acidosis by hyperventilation. Conversely, those dying showed an increasing pCO_2 with decreasing pH (Fig. 1). *Discussion:* There may be several explanations for this observation. Patients with

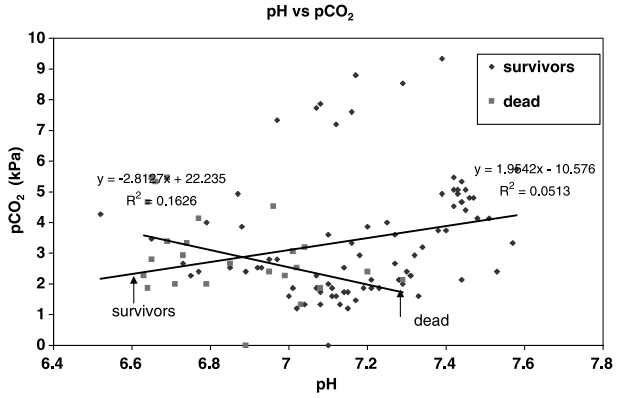

FIG. 1.

reduced ability to hyperventilate may have a higher risk of dying. Another explanation could be that the patients who die are admitted in a later stage of the poisoning. However, the time from intake to admission between the two groups did not differ significantly: The median time from intake to admission for the survivors was 27 hrs and in the dead patients 24 hrs. Among survivors 23 out of 86 (27%) also drank ethanol, while 2 of the 25 (8%) dying did this. *Conclusion:* The present results indicate that ability to compensate metabolic acidosis by hyperventilation is associated with increased survival in methanol poisoning.

40. Place of Oesogastric Endoscopy After Accidental Ingestion of Corrosive Products in Children with No Clinical Symptoms

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In our hospital, oesogastric endoscopy (OGE) is always performed after corrosive ingestion. However, this protocol has been challenged when the child presents no with clinical symptoms. *Objective:* to determine the value of systematic OGE in all cases of corrosive ingestion in children with no clinical symptom. *Method:* retrospective analysis (1995–2002) of children admitted for corrosive ingestion with no clinical symptoms. *Results:* within 1458 children, 23 asymptomatic on admission were found to have oesogastric lesions by OGE performed within 24 h. Oesophagogastric injuries were only found when the corrosive products had a pH less than 2 or greater than 13 or in cases involving strong oxidants (Table 1). *Conclusion:* systematic oesophagogastric endoscopy is probably not indicated in every case of asymptomatic child after corrosive ingestion. However the absence of clinical symptom, especially oral or laryngo pharyngeal injury does not always exclude the existence of lower digestive tract injury. The characteristics of ingested the ingested corrosive product have also to be taken into consideration. *Reference:* 1. Hawkins DB, Demeter MJ, Barnett TE. Caustic ingestion: controversies in management. A review of 214 cases. *Laryngoscope* 1980; 90:98–109.

TABLE 1
Distribution of patients with oesogastric lesion by class of injury and corrosive substance

Injury class (1)	Nb of patients	%	Corrosive substance
I	10	44	Sulfamic acid, formic acid, sodium hypochloride, solvent
II a	11	48	Sodium hydroxide, phosphoric acid, quaternary ammonium, hydrogen peroxide
II b	1	1	Ammonium bifluoride
III	1	1	Sodium hydroxide

41. Corrosive Ingestion: The Evidence Base. Controversy in Dilution and Neutralization Therapy

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Objective: To review the basis for management of corrosives ingestion. *Methods:* Reports concerning caustic ingestions published between 1994 and 2004 were searched in Medline database (English, German, French, Spanish and Russian). Results of studies were compared with recommendations in recent textbooks of toxicology. *Results:* Total five experimental studies were found; all carried out by Homan et al. Early dilution therapy with water or milk was shown to reduce acute alkali and acid injury of the oesophagus. The histopathologic outcome parameters have documented that early neutralization therapy with weak acid (orange juice or cola) was effective in decreasing alkaline tissue injury (1). Similar effect had weak $NaHCO_3$ neutralization after acid injury. No temperature elevation above basal temperature was noted (2). Only one clinical study compared effect of early dilution in patients who drank water or milk immediately after the ingestion of caustic soda with those, who did not. The difference in incidence of oesophageal stenosis was not significant (3). No case reports, bringing suspicion on acute deaths caused by inappropriate management of corrosives ingestions with neutralization therapy have been found in the literature search. Most of recent toxicology textbooks and review articles recommend dilution therapy with 100–200 ml milk or water. Higher amounts of diluents could increase the risk of vomiting, aspiration or moving the corrosive distally to duodenum. Dilution is only rarely considered contraindicated. On the other hand, neutralization is almost unequivocally contraindicated,

based on in vitro studies reporting thermal reactions (4). Positive effect of neutralisation described another in vivo study (5). Thermal effects have not been observed in vivo probably because volume of surrounding tissue and local blood flow may be sufficient to dissipate any heat produced from the reaction. *Conclusion:* Damaging effect of even mild neutralization had been suspected, but has not been confirmed in experimental in vivo studies and case reports in past 10 years. Additional observations are needed, as there are not enough experimental and clinical data to prohibit this procedure. *References:* 1. Homan CS, Singer AJ, Henry MC, et al. Thermal effects of neutralization therapy and water dilution for acute alkali exposure in canines. *Acad Emerg Med* 1997; 4:27–32. 2. Homan CS, Singer AJ, Thomajan C, et al. Thermal characteristics of neutralization therapy and water dilution for strong acid ingestion: an in-vivo canine model. *Acad Emerg Med* 1998; 5:286–292. 3. Mamede RC, De Mello Filho FV. Treatment of caustic ingestion: an analysis of 239 cases. *Dis Esophagus* 2002; 15:210–213. 4. Rumack BH, Burrington JD. Caustic ingestions: a rational look at diluents. *J Toxicol Clin Toxicol* 1977; 11:27–34. 5. Leape LL. New liquid lye drain cleaners. *J Toxicol Clin Toxicol* 1974; 7:109–114. Acknowledgement: Supported by MSM0021620807.

42. Intoxication with Alpha-Lipoic Acid: Case Reports and Toxicokinetic Analysis

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Objective: Alpha-lipoic acid (ALA) is an OTC preparation used in the treatment of diabetic polyneuropathy or as antioxidative dietary supplement. Although ALA causes severe and even fatal intoxications, few pharmacokinetic data so far been published and almost nothing is known about its toxicokinetic properties. In this presentation clinical representation of six patients intoxicated with ALA are analyzed and toxicokinetic parameters are derived from two suicidal poisonings. *Methods:* (a) The clinical courses of six patients, who ingested >200 mg ALA per kg body weight and who were reported to poison information centres were monitored by follow-up reports. (b) For toxicokinetic analysis plasma concentrations of ALA from a 69 year old male, who ingested ALA twice within four months in a dose of 340 mg/kg and 510 mg/kg respectively, were measured by RP-HPLC before, during and after haemodialysis until 72 hours after ingestion. Oral bioavailability, elimination half-life, volume of distribution and efficacy of haemodialysis were computed based on linear kinetics and compared to pharmacokinetic data published elsewhere. *Results:* In all patients symptoms of intoxication encompassed disturbances of the CNS ranging from agitation to convulsions, increasing lactate acidosis, hyperglycaemia and disseminated intravascular coagulation occurring within 1 to 6 hours after ingestion. In at least three cases lactate acidosis was treated with haemodialysis or haemofiltration, respectively. Quantification of ALA in plasma samples obtained from a single patient with an ingested 510 mg ALA per kg allowed estimation of a prolonged elimination half-life ranging from 80 to 160 min, which was not significantly reduced by high-flow haemodialysis. Additionally, ongoing absorption was observed until approx. 40 hours after ingestion. Estimated oral bioavailability in intoxication (26.7% at dose 340 mg/kg) did not significantly differ from that found under therapeutic dose (29.1% at dose 2.7 mg/kg), indicating non-saturable absorption of ALA with a substantial hepatic first-pass effect. *Conclusion:* (a) Occurrence and severity of symptoms are more related to peak plasma concentration of ALA than to ingested dose. (b) Early gastric emptying and repeated application of charcoal/cathartic appears to be of major importance in reducing peak plasma concentration of ALA and the occurrence of delayed absorption, thus reducing severity and duration of symptoms. (c) Haemodialysis or haemofiltration are ineffective in enforced elimination of ALA, but may be lifesaving in ALA poisonings with severe lactic acidosis. *References:* Teichert J, Kern J, Tritschler HJ, Ulrich H, Preiss R, Teichert J. *Int J Clin Pharmacol Ther* 1998; 36(12):625–628. Hermann R, Ruus P, Preiss R. *J Clin Pharm* 2003; 43:1257–1267.

43. Pharmacokinetics of Digoxin-Like Substances in the Plasma of Patients with Yellow Oleander (*Thevetia peruviana*) Self Poisoning

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Objective: Self-poisoning with seeds from the yellow oleander tree (*Thevetia peruviana*) occur worldwide, but is particularly common in Sri Lanka. The pharmacokinetics of the cardenolides in yellow oleander poisoning, and the effect of administration

of anti-digoxin Fab, have not been reported. *Methods:* Serial blood samples were obtained from 19 patients admitted to a rural hospital in Sri Lanka with acute yellow oleander poisoning. Because yellow oleander's cardenolides are structurally similar to those of digoxin, digoxin-like substances (DLS) were measured in plasma by immunoassay to estimate the concentration of yellow oleander cardenolides. *Results:* Serial samples were obtained for 37–77 hours (median 63 hours) post-ingestion. Severe cardiac dysrhythmias were reversed in 3 patients at ~20 hours post-ingestion using anti-digoxin Fab with a pre-treatment DLS concentration of 1.54–1.74 ng/mL. This concentration increased more than two-fold following administration of Fab, consistent with cardenolide redistribution from the extravascular space and neutralisation, which has also been reported in digoxin poisoning. The DLS concentration was lower than this in all other patients at 20 hours except one patient (1.59 ng/mL at 22 hours) who did not require anti-digoxin Fab. DLS concentrations were highly variable in four patients, making interpretation difficult, so they were not considered further. In the remaining 12 patients, the DLS measured in plasma increased until 12–22 hours post-ingestion. The peak concentration was not related to the history of the number of seeds ingested. Between approximately 20 and 40 hours post ingestion, DLS concentrations decreased or plateaued. The delay in peak concentration and minimal fall plasma concentration may suggest ongoing absorption until this stage. Beyond 40 hours, concentrations generally decreased which may represent the elimination phase of cardenolides, with a corresponding median apparent plasma elimination half-life of 34 hours (range 16.4–56.1). The possibility of ongoing absorption and distribution during this elimination phase could not be excluded. *Conclusion:* Self-ingestion of yellow oleander seeds is associated with unpredictable absorption of cardenolides and a delayed peak concentration. This is also associated with a late onset of cardiotoxicity, and late onset of cardiotoxicity (~20 hours). In some patients, DLS concentrations were highly unpredictable. Delayed absorption and unpredictable concentrations may relate to erratic cardenolide release from the cellulose matrix of the ingested seeds.

44. Mortality and Causes of Death in a 20 Year Follow-Up of Patients Treated for Self-Poisonings in Oslo

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Objective: Long term data on prognosis in patients admitted for self-poisonings are scace. We therefore studied mortality rate, causes of death and risk factors for committing suicide in this patient population. *Methods:* All patients discharged from medical departments in Oslo in 1980 after treatment for self poisoning were included; n=946, 51% females (1). Median age was 31 years. Seventeen percent were considered suicidal attempts upon admission, 24% among the non-abusers and 8% among the abusers. The toxic agents were medication, alcohol or narcotics irrespective of suicidal intent. The mortality in this cohort was compared to that in the general population of Norway, and standard mortality ratios (SMRs) were computed. *Results:* Follow up at 20 years showed that 338 (35.7%) of the patients were dead, (30.2% among females and 45.1% among males. There were 62 (6.6%) who had completed suicide (6.9% among females, 6.3% among males). The suicide rate among those who were considered suicidal upon admission was 14.9%. There was a significantly higher risk of death of all causes except for cancer for these patients during the whole 20 year follow up period. Logistic regression analyses showed that male sex, higher age, lower levels of consciousness, drug abuse and lower social class were independent predictors of death, whereas a suicidal motive upon time of admission was the only independent predictor of suicide. *Conclusion:* The mortality rate after hospitalisation for self poisoning is comparable to many malignant conditions. The risk of suicide and other causes of death is higher than expected during the whole 20 year follow-up period. *Reference:* Jacobsen D, Frederichsen PS, Knutsen KM, Sorum Y, Talseth T, Odegaard OR. A prospective study of 1212 cases of acute poisoning: general epidemiology. *Hum Toxicol* 1984; 3(2):93–106.

45. Mechanism of Toxicity of Commercial Glyphosate Formulatons: How Important is the Surfactant?

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Commercial glyphosate concentrate formulations (CGCFs) comprise the active ingredient, surfactants intended to improve spreading on plant surfaces and penetration of the waxy plant cuticle, and various minor ingredients (dye, silicone antifoam) conferring negligible toxicity. Typical formulations historically contain 41% glyphosate (GLY) with 10–20% loadings of ethoxylated tallowamine surfactant. GLY is an inhibitor of the enzyme enolpyruvate-shikimate-3-phosphate-synthase (EPSPS),

responsible for aromatic amino acid synthesis in plants and lower organisms. This pathway does not exist in mammalian species. GLY has a low mammalian toxicity (rodent LD-50>5000 mg/kg) and has been administered intravenously to humans as an anti-fungal agent with no apparent toxicity. Despite the low toxicity of GLY, CGCFs are well known to cause serious illness following intentional ingestion, leading some to conclude that the surfactant is likely responsible for the toxicity of these products. Further, based on the clinical presentation of multi-organ failure with intractable cardiovascular collapse, some have speculated that GLY or the surfactant may impede mitochondrial function. In 2001, results were published suggesting that GLY was an ''endocrine disrupter'' on the basis of inhibition of steroidogenesis in cultured Sertoli cells. We were able to demonstrate that these findings were the result of direct cytotoxicity of the surfactant. Further studies undertaken with mitochondrial dye JC-1 demonstrated that decreased steroidogenesis was coincident with mitochondrial membrane damage and the subsequent loss of mitochondrial membrane potential. This effect was demonstrable with a variety of surfactant molecules. The toxicology literature contains occasional case reports of surfactant (shampoo, etc.) ingestions having clinical presentations similar to those observed with CGCFs. Further, many herbicides, particularly those lacking a specific target in mammalian species, possess very low intrinsic mammalian toxicity but nonetheless produce substantial toxicity following ingestion of commercial formulations. Despite the high molecular weight of many surfactant materials, limited data suggest that bioavailability by the oral route may be substantial. *Conclusion:* The toxicity of CGCFs appears to result from surfactant mediated uncoupling of mitochondrial oxidative phosphorylation; an effect seen with a variety of surfactant types. Clinical experience with other surfactant-containing products strongly suggests that surfactant-mediated mitochondrial toxicity may be a common pathway responsible for much of the clinical toxicity observed following ingestion of herbicide formulations containing low-toxicity active ingredients. *References:* Walsh LP, McCormick C, Martin C, Stocco D. Roundup Inhibits Steroidogenesis by Disrupting Steroidogenic Acute Regulatory (StAR) Protein Expression. *Envir Health Perspec* 2000; 108:769–776. Levine SL, Farmer DR, Heydens WF, Han Z, Wall C, Papadopoulos V. Non-specific alteration of steroidogenesis in vitro by supra-physiological levels of surfactant. Society of Environmental Toxicology and Chemistry, 22nd annual meeting abstracts, 2003.

46. Glyphosate: Features and Management of Poisoning with Commercial Formulations

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Introduction: Glyphosate is a non-selective herbicide that is used extensively since its mechanism of action is plant-specific and it has a favourable environmental safety profile. Moreover, its use is likely to increase since it is one of the first herbicides against which crops have been genetically modified to increase their tolerance. Most commercial glyphosate formulations contain the isopropylamine glyphosate salt (up to approximately 50%) in aqueous solution plus a surfactant (up to 30%) as a wetting agent. Exposure to these products is relatively common but significant toxicity is rare and almost exclusively follows ingestion of a concentrated formulation (typically 41% glyphosate as the isopropylamine salt and 15% polyoxyethyleneamine). The toxicity of glyphosate-containing herbicides has recently been reviewed (1). *Features:* Ingestion of dilute, ready-to-use, amateur formulations is likely to result only in nausea, vomiting and diarrhoea. Small amounts (up to 30 mL) of concentrated preparations have not caused severe systemic effects in adults but may cause burning in the mouth and throat, hypersalivation, nausea, vomiting and diarrhoea. Ingestion of more than 85 mL of a concentrated formulation is likely to cause significant toxicity and in these cases there is a reasonable correlation between the amount ingested and the likelihood of serious systemic sequelae or death. Advancing age is also associated with a less favourable prognosis. Upper gastrointestinal corrosive effects are common, typically oesophagitis and/or gastritis. In more severe cases gastrointestinal haemorrhage may precipitate hypovolaemic shock. Subsequent renal and hepatic impairment, systemic acidosis and/or impaired conciousness may reflect reduced organ perfusion though a direct toxic effect of glyphosate or surfactant may contribute. Seizures may occur. Respiratory distress is likely in severely poisoned patients and may be contributed to by aspiration, though non-cardiogenic pulmonary oedema (Adult Respiratory Distress Syndrome) is recognised. Electrocardiographic abnormalities occur in up to 20% of cases, usually sinus tachycardia and/or non-specific ST-T wave changes, though sinus bradycardia, atrioventricular block and ventricular arrhythmias are recognised. Substantial ingestion of newer products containing the potassium salt of glyphosate may cause hyperkalaemia or exacerbate hyperkalaemia occurring in association with renal failure and/or acidosis. Dermal exposure to ready to use glyphosate formulations can cause irritation and photo-contact dermatitis has been reported occasionally; these effects are probably due to a preservative in the preparation. Severe skin burns are very rare. Inhalation is a minor route of exposure but spray mist may cause oral or nasal discomfort, an unpleasant taste in the mouth, tingling and throat irritation. Eye exposure may lead to mild conjunctivitis, and superficial corneal injury is possible if irrigation is delayed or inadequate. *Management:* Management is symptomatic and supportive and skin decontamination with soap and water after removal of

contaminated clothing should be undertaken in cases of dermal exposure. *References:* 1. Bradberry SM, Proudfoot AT, Vale JA. Glyphosate poisoning. *Toxicological Reviews* 2004; 23. In press.

47. Pyrethroids: Mechanisms of Toxicity, Features and Management

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Introduction: Pyrethroids are synthetic derivatives of natural insecticidal pyrethrins found in chrysanthemum flowers. They were developed primarily to overcome the instability of pyrethrins in light and air. Since the 1970s their use has increased to account for nearly a quarter of the worldwide insecticide market. The main reasons for their success are effectiveness at very low use rates, comparatively low mammalian toxicity and lack of bioaccumulation in humans or the environment. *Mechanisms of Toxicity:* The primary action of pyrethroids is on the voltage-sensitive sodium channel leading to prolonged excitation in the absence of cytotoxicity (1). The proportion of sodium channels affected and hence the degree of hyperexcitability is dose-dependent whereas the duration of the hyperexcitable state and hence the nature of the effect is structure dependent: a fine tremor and reflex hyperexcitability is primarily caused by compounds lacking an alpha-cyano group (T or type I syndrome) while those containing an alpha-cyano group produce choreoathetosis, seizures and sympathetic activation (C/S or type II syndrome) (2). Some pyrethroids produce both syndromes. Other target sites may be important in the development of pyrethroid toxicity, in particular voltage-sensitive chloride and calcium channels and possibly peripheral-type benzodiazepine receptors (1,2). Pyrethroids are rapidly metabolized by carboxyesterases which may be inhibited by some organophophates. Synergistic toxicity has been described after high-dose administration in animal studies, however, this has so far not been observed in humans (3). In occupational exposure, acetyl cholinesterase depression caused by organophosphates does not appear to be influenced by pyrethroids (4), but pyrethroid half life may be prolonged by organophosphates (5). *Clinical Features:* The most common symptom in occupational pyrethroid exposure is paraesthesia of the facial skin (3,6,7). This effect is due to direct stimulation of cutaneous nerve endings, occurs at very low doses, is self-limiting and not associated with systemic toxicity (8). Symptoms of systemic poisoning are primarily seen following accidental or, more commonly, intentional ingestion of concentrated pyrethroid formulations. In a series of 573 cases three degrees of severity were described with mild cases showing mainly headaches, dizziness, nausea, anorexia and fatigue. In moderate poisoning disturbances of consciousness and muscular fasciculations were seen whereas severe poisoning was characterised by convulsions, coma and pulmonary oedema (9). Only seven fatalities occurred and this generally favourable outcome of pyrethroid poisoning has been confirmed in other case series (10,11). Many severe cases are characterised by the development of pulmonary oedema and/or aspiration pneumonitis. Since these are not seen in animal toxicology studies with pyrethroids it raises the question whether other formulation constituents such as surfactants and organic solvents contribute to the severity of intoxication (11). *Management of Poisoning:* Due to their highly lipophilic nature most pyrethroids are slow skin penetrants and decontamination with water and detergents is an important first-aid measure. Concentrated formulations can be severe eye irritants and require rapid, prolonged irrigation and assessment for corneal damage. In cases of ingestion a benefit of gastric decontamination has not been demonstrated (12). Induction of vomiting is contraindicated because of the high solvent and surfactant content of most formulations, and it would seem prudent to restrict gastric decontamination to cases where a severe outcome is anticipated. The use of atropine has been advocated to treat pulmonary oedema (2,9), however, its benefit is questionable and the therapy is not without risk. Experimentally, ion channel or membrane-stabilizing drugs (e.g. lidocaine, phenytoin, phenobarbitone, pentobarbitone, diazepam, mephenesin, urethane, clomethiazole) have been used alone or in combination (2) but no clinical data are available regarding their effectiveness in human poisoning. *Conclusion:* Despite their widespread use reports of serious pyrethroid poisonings are comparatively rare. Where they occur they are principally due to ingestion of concentrated formulations often with the intent of self harm. In contrast, occupational exposure is commonly associated with paraesthesia of the face, but this is not associated with systemic toxicity. Although structurally similar, pyrethroid effects on ion channels are heterogenous and future research should be directed towards identifying their relative importance in pyrethroid toxicity. This would also serve as a guidance for clinical trials to study the effectiveness of specific treatments. *References:* 1. Soderlund DM, Clark JM, Sheets LP, et al. Mechanisms of pyrethroid neurotoxicity: implications for cumulative risk assessment. *Toxicology* 2002; 171:3–59. 2. Ray DE, Forshaw PJ. Pyrethroid insecticides: poisoning syndromes, synergies and therapy. *J Toxicol Clin Toxicol* 2000; 38:95–101. 3. Chen S, Zhang Z, He F, et al. An epidemiological study on occupational acute pyrethroid poisoning in cotton farmers. *Br J Ind Med* 1991; 48:77–81. 4. He F, Chen S, Tang X, et al. 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subjects engaged in packaging pyrethroids. *Br J Ind Med* 1988; 45:548–551. 7. Zhang Z, Sun J, Chen S, et al. Levels of exposure and biological monitoring of pyrethroids in spraymen. *Br J Ind Med* 1991; 48:82–86. 8. Wilks MF. Pyrethroid-induced paresthesia—a central or local toxic effect? *J Toxicol Clin Toxicol* 2000; 38:103–105. 9. He F, Wang S, Liu L, et al. Clinical manifestations and diagnosis of acute pyrethroid poisoning. *Arch Toxicol* 1989; 63:54–58. 10. Peter JV, John G, Cherian AM. Pyrethroid poisoning. *J Assoc Physicians India* 1996; 44:343–344. 11. Yang PY, Lin JL, Hall AH, et al. Acute ingestion poisoning with insecticide formulations containing the pyrethroid permethrin, xylene and surfactant: a review of 48 cases. *J Toxicol Clin Toxicol* 2002; 40:107–113. 12. Bateman DN. Management of pyrethroid exposure. *J Toxicol Clin Toxicol* 2000; 38:107–109.

48. Fumigant Toxicity: Much to Study

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Background: Fumigants applied to the soil for nematode, insect, weed and fungi control have been used for decades to enhance agricultural food production. Structural fumigation has been performed to control wood-boring insects. Historically, the toxicity to humans and/or the environment has caused the continuous introduction of new fumigants that eventually are discontinued or banned. *Discussion:* Halogenated substances have been a mainstay for soil and structural fumigation. This fact is still true today. For example, commonly used fumigants include methyl bromide, dichloropropene, sulfuryl fluoride and chloropicrin. These fumigants are similar both structurally and mechanistically to many other solvents to which toxicologists have significant clinical and regulatory experience. Acutely, exposures have resulted from occupational exposures during application or post-application off-gassing, hazardous materials incidents during transport, and drift from the application site to neighboring residential or industrial sites. In the case of structural fumigation, exposures by reentry without adequate ventilation or by the passage of fumigant through conduits to adjacent structures have caused many fatalities. Suicidal patients using fumigants have been rare, but they have increased our knowledge base. The acute toxicities can resemble halogenated solvents, with the potential for CNS depression and seizures, cardiovascular dysrhythmias, pulmonary edema, and hepatic and renal failure. Permanent neuropsychiatric and neuropathic sequelae may result. The diagnosis following acute or chronic low level exposures is more challenging, as onset may be days after exposure and initially may mimic acute gastroenteritis and other flu-like syndromes. Toxicological understanding of chronic occupational exposures is even less clear. Many of the fumigants undergo cytochrome oxidation to reactive intermediates that may result in chronic toxicity and carcinogenesis. Inhibition of sulfhydryl-containing enzymes may be one mechanism of toxicity. Many of these agents cause glutathione depletion and act as alkylating agents. In the case of methyl bromide, many of the clinical features and findings resemble metal toxicity such as methyl mercury. Research is ongoing to find better bio-monitoring tools. Albumin and hemoglobin adducts for methyl bromide have been identified. Pharmacogenetics and pharmacogenomics will help unravel the individual variability that is seen in cases of chronic toxicity. Despite a number of proposed treatments, patient management remains supportive. Additionall, the use of fumigants has impacted the environment. The 1998 Montreal Protocol has banned methyl bromide because of ozone depletion. Air and water contain low levels of fumigants. Foods contain residues from these agents. The long term impact of these low level exposures on the environment and human health creates another field of study for the toxicologist. *Conclusions:* Fumigants are expected to continue in widespread use in agriculture. The methyl bromide ban may lead to newer agents that will retain many of the unsolved toxicological issues and possibly new ones, as occurred when aerosolized leather protectors had their formulations changed to prevent ozone depletion. Clinical toxicologists will be part of the team for the acute treatment and epidemiological study of the fumigant poisoned patients and workers. Clinical toxicologists should strengthen their ties with research scientists and regulatory agencies studying fumigant toxicity, to assist in policies that will protect the environment thereby reducing inadvertent human exposure.

49. Bipyridyl Herbicides: Mechanisms of Toxicity, Features and Management

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Background: Diquat and paraquat contain a bypiridyl ring and exist as divalent cations associated with anions such as bromide and chloride. They are non-selective contact herbicides. Compared with paraquat, diquat is used less widely and poisoning is

less common. *Mechanisms of Toxicity:* Diquat and paraquat exert their cellular toxicity by, firstly, undergoing oxidation and reduction in a cyclical manner (hence the term redox cycling) to produce free radicals such as superoxide anion ($O_2^{\cdot -}$) and, secondly, by depleting NADPH. Under anaerobic conditions NADPH-dependent microsomal flavoprotein reductase reduces diquat and paraquat from their cations to form a stable free radical. In the presence of oxygen the radical will immediately reform the cation with the concomitant production of superoxide. Provided there is a continuous supply of electrons and oxygen is present, diquat and paraquat will rapidly cycle from oxidized to reduced forms with the continuous production of superoxide anions. The superoxide anions produced from this cycle react with each other forming hydrogen peroxide and molecular oxygen, a reaction that may occur spontaneously or via the enzyme superoxide dismutase. Under normal circumstances hydrogen peroxide is detoxified by catalase and glutathione peroxidase, but when such protective mechanisms are overwhelmed it is free to cause devastating effects on cells. In the presence of iron, the superoxide anion radical reacts with hydrogen peroxide generating the even more potent hydroxyl radical which can attack the lipid chains of biological membranes initiating lipid peroxidation that results in membrane damage and ultimately cell death. Significant depletion of NADPH occurs by two mechanisms. Firstly, redox cycling occurs to such an extent that NADPH levels within cells are decreased. Secondly, NADPH is utilized in the detoxification of hydrogen peroxide and lipid hydroperoxides via the glutathione peroxidase and reductase enzyme systems. It is postulated that depletion of NADPH not only disrupts essential physiological and biochemical functions but also renders cells more susceptible to lipid peroxidation. Unlike paraquat, diquat is not accumulated by the lung where it has a half-life five times shorter than paraquat. Experimental evidence suggests that the concentration of paraquat in lung cells causes a severe redox stress that leads eventually to sustained NADPH depletion. This by itself, or in combination with lipid peroxidation, initiates the cascade of biochemical events that lead to cell death. The biochemical effects described above probably also occur in other organs in addition to the lung. It is likely that death occurring within a few hours of diquat or paraquat ingestion is due to massive depletion of NADPH with consequent disruption of energy metabolism particularly in the liver. On the other hand, the clinical course observed in those suffering from less severe intoxication is in keeping with cell membrane destruction initiated by lipid peroxidation. *Features of Diquat Poisoning (1):* Local and systemic effects have been observed following diquat exposure, systemic features being associated primarily with cases of acute ingestion. Ocular burns, corneal scarring and epistaxis have been reported following eye and nasal exposure; prolonged skin contact with diquat may cause full thickness skin burns, disturbance of nail growth and shedding of the nail. Ingestion causes oral mucosal irritation and is followed by abdominal pain, epigastric tenderness, diarrhoea and hepatic dysfunction. Paralytic ileus may contribute to hypovolaemic shock via fluid accumulation in distended bowel loops. Circulatory collapse may cause acute tubular necrosis, although acute renal failure has been described in the absence of hypovolaemia, suggesting a direct renal toxic effect. Death may follow hypovolaemic shock or ventricular tachycardia/fibrillation; respiratory arrest has complicated the development of bronchopneumonia or the adult respiratory distress syndrome. The ingestion of a substantial amount of diquat (>6 g) may cause death within 24 hours. *Features of Paraquat Poisoning (2):* The local effects of paraquat on the cornea, conjunctiva, skin, upper alimentary tract (particularly the oesophagus) and larynx depend on the concentration of the herbicide in the formulation. Inhalation of spray may cause pain in the throat and epistaxis. Splashes in the eye cause blepharospasm and lacrimation; severe inflammation of the cornea and conjunctiva may follow after 12–24 h and lead to ulceration. Dermal exposure may cause erythema, blistering, and ulceration of the skin and concentrated solutions may cause gross deformity of the nails and nail loss. When ingested, painful ulcers in the mouth and on the tongue are characteristic and sloughing of the oropharyngeal mucosa, inability to swallow saliva, dysphagia and dysphonia are common. Prominent pharyngeal membranes have been reported and perforation of the oesophagus may result in mediastinitis, surgical emphysema and pneumothorax. Subsequent developments are dose-related. Three degrees of systemic toxicity may usefully be distinguished (2). Mild poisoning follows the ingestion or injection of <20 mg of paraquat ion/kg body weight (Group 1). Patients are asymptomatic or develop only vomiting and diarrhoea. Full recovery occurs but there may be a transient fall in the gas transfer factor and vital capacity. Moderate to severe poisoning follows the ingestion or injection of 20–40 mg of paraquat ion/kg body weight (Group 2). Patients suffer vomiting and diarrhoea and develop generalized symptoms indicative of systemic toxicity. Pulmonary fibrosis develops in all cases but recovery may occur. In addition, renal failure and, sometimes, hepatic dysfunction may supervene. Death occurs in the majority of cases but can be delayed for 2 or 3 weeks. Acute fulminant poisoning follows the ingestion of more than (usually considerably in excess of) 40 mg of paraquat ion/kg body weight (Group 3). In addition to nausea and vomiting, there is marked ulceration of the oropharynx with multiple organ (cardiac, respiratory, hepatic, renal, adrenal, pancreatic, neurological) failure. In this group the mortality is 100%. Death commonly occurs within 24 h of ingestion of paraquat and is never delayed for more than one week. *Management of Diquat and Paraquat Poisoning:* Gut decontamination may be considered in patients who present within one hour of ingestion, though there is no clinical evidence that this approach is of benefit. Supportive measures including fluid and electrolyte replacement should be employed, and are of particular importance in diquat poisoning. There is no evidence that haemodialysis, haemofiltration or haemoperfusion remove clinically significant amounts

of diquat or paraquat, thereby preventing a fatal outcome in severe cases. Based on an understanding of the mechanisms of toxicity, further management should theoretically be directed towards preventing the accumulation of diquat and paraquat in key organs. However, there is no evidence that antioxidants or anti-inflammatory agents are effective clinically (3,4). *References:* 1. Jones GM, Vale JA. Mechanisms of toxicity, clinical features, and management of diquat poisoning: a review. *J Toxicol Clin Toxicol* 2000; 38:123–128. 2. Vale JA, Meredith TJ, Buckley BM. Paraquat poisoning clinical features and immediate general management. *Hum Toxicol* 1987; 6:41–47. 3. Bateman DN. Pharmacological treatments of paraquat poisoning. *Hum Toxicol* 1987; 6:57–62. 4. Suntres ZE. Role of antioxidants in paraquat toxicity. *Toxicology* 2002; 180:65–77.

50. Chlorophenoxy Herbicides: Mechanisms of Toxicity, Features and Management

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Introduction: Chlorophenoxy herbicides are chemical analogues of plant hormones and produce uncontrolled and lethal growth in target plants. They are used primarily to control broad-leaved weeds in pastures, lawns, cereal crops and along public rights of way. Structurally they comprise an aliphatic carboxylic acid moiety attached to a chlorine- or methyl-substituted aromatic ring. The most commonly encountered herbicide of this class is 2,4-dichlorophenoxyacetic acid (2,4-D). The toxicity of these herbicides has been reviewed recently (1,2). *Mechanisms of Toxicity:* Chlorophenoxy herbicides cause dose-dependent cell membrane damage. Within the central nervous system this results in disruption of the blood-brain barrier and neuronal membrane transport. Since chlorophenoxy herbicides are related structurally to acetyl coenzyme A, they can form analogues of this molecule and so interfere with its metabolism including the synthesis of acetylcholine, with the formation of false messengers such as 2,4-D-ACh. Disruption of both membrane transport and acetyl-CoA metabolism contributes to the uncoupling of oxidative phosphorylation, an additional mechanism of toxicity. *Features:* Most cases of serious poisoning involve deliberate ingestion of products containing either 2,4-D alone or 2,4-D in combination with other chlorophenoxy herbicides; 69 such cases have been reported in the literature since 1962. Vomiting is a common early feature and may be accompanied by buccal irritation, abdominal pain and diarrhoea. Gastrointestinal haemorrhage is recognised in more severe cases, though corrosive effects are probably caused more by the coformulants than the chlorophenoxy compound. Hypotension results from a combination of fluid loss, vasodilation and possibly direct myocardial toxicity. There may be electrocardiographic conduction abnormalities and/or arrhythmias. Coma is a characteristic feature of severe poisoning and is associated frequently with respiratory distress and occasionally pulmonary oedema. Upper motor neurone involvement is suggested in some cases by the presence of hypertonia, hyperreflexia, clonus and/or extensor plantar responses. Lower motor neurone signs and features of a generalised myopathy may also be seen. Other neurological features include nystagmus, miosis, ataxia, cerebral oedema and convulsions. Metabolic effects include acidosis, hyperthermia, hepatic and renal damage and rhabdomyolysis. Although the prognosis is poor in those who rapidly become shocked and comatose, full recovery can ensue even in those with initially severe toxicity and prolonged neuromuscular involvement. Systemic toxicity following topical or inhalational exposure is rare though local irritant effects are recognised. *Management:* As there is some in vitro evidence that chlorophenoxy herbicides are adsorbed to activated charcoal (3,4), the administration of activated charcoal 50–100 g may be considered as a means of reducing gastrointestinal absorption in patients presenting within one hour of a potentially life-threatening ingestion. Management is otherwise symptomatic and supportive. If diagnostic confirmation is necessary, the concentration of herbicide may be measured in plasma, though such assays are not available widely. Enhanced elimination of the chlorophenoxy compound by urine alkalinization or haemodialysis should be considered in severely poisoned patients. A detailed review of the rationale and evidence supporting urine alkalinization in chlorophenoxy herbicide poisoning has recently been undertaken and highlights the paucity of reliable data in this field (5) with only a single case (published in two separate articles) providing adequate information for critical review (6,7). This demonstrates that although urine pH manipulation can modify renal chlorophenoxy herbicide elimination, the clearance achieved is critically dependent on urine flow. The maximum 2,4-D clearance of 63 mL/min observed at urine pH 8.3 in this patient (7) would have required a urine flow rate of approximately 600 mL per hour to compare favourably with the clearance achieved in other cases with haemodialysis (56.3–72.9 mL/min) (8). In patients severely poisoned with chlorophenoxy herbicides, haemodialysis is the preferred treatment since it not only avoids the need for urine pH manipulation but also the administration of large volumes of intravenous fluid to physiologically unstable patients. *References:* 1. Bradberry SM, Watt BE, Proudfoot AT, Vale JA. Mechanisms of toxicity, clinical features, and management of acute chlorophenoxy herbicide poisoning: a review. *J Toxicol Clin Toxicol* 2000; 38:111–122. 2. Bradberry SM, Proudfoot AT, Vale JA. Poisoning due to chlorophenoxy herbicides. *Toxicol Rev* 2004; 23:65–73. 3. Grover R, Smith AE. Adsorption studies with the acid and dimethylamine forms of 2,4-D and dicamba. *Can J Soil Sci* 1974; 54:179–186. 4. Belmouden M, Assabbane A, Ichou YA. Adsorption characteristics of a phenoxy acetic acid

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51. Exposure to Mixtures of Pesticides in Food

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There has, for some years, been concern about exposure to mixtures of synthetic chemicals *inter alia* pesticides and this is sometimes called the ''cocktail effect.'' United States Food Quality Protection Act (1996), (FQPA): this act of the US Congress mandated that all sources of exposure to pesticides and co-exposure to more than one pesticide should be considered during risk assessment. The FQPA also introduced the terms, cumulative risk assessment and aggregate risk assessment, the former referring to risk assessment of more than one pesticide at a time and the latter to risk assessment of pesticides from all sources of exposure. Thus the term cumulative risk assessment does not refer to pharmacological accumulation but rather to the concept that assessment of the effects of exposure shall not be carried out in isolation. Risk assessment should thus take account of co-exposure to many pesticides and thus address the ''cocktail effect.'' *Mixture Toxicology:* mixture toxicology has been bedevilled by confusion of terminology. The tendency nowadays is to use the terminology of Cassee et al. (1). Fundamental considerations of toxicology suggest that pesticides with the same toxicological action should exhibit dose additivity (simple similar action), whereby in a mixture each pesticide contributes to the total toxicity of the mixture in proportion to the dose adjusted for the potency of the pesticide. Pesticides with different mechanisms of toxicity will exhibit simple dissimilar action (effect addition). Neither simple similar action nor simple dissimilar action are considered interactions, as the pesticides in the mixture do not modulate one another's actions. Interactions, where the pesticides do modulate one another's actions, comprise potentiation (synergy) and antagonism. The default assumption for cumulative risk assessment is that interactions will not usually occur at doses of pesticide produced by exposure to residues in food and the environment. *Cumulative Risk Assessment:* In order to carry out cumulative risk assessment it is necessary firstly to identify groups of pesticides with common mechanisms of action (common mechanism groups [CMGs]). Secondly the relative potencies of pesticides in that group must be measured and thirdly data on the intake of all the pesticides in that group must be obtained. Common mechanism groups (CMGs): the biggest scientific problem in cumulative risk assessment is the identification of CMGs. In some cases, e.g. organophosphates, there is little difficulty identifying CMGs, although even here there are compounds (ethephon, tolclofos-methyl) which have some of the properties of the group, but are toxicologically atypical. In other cases, for example endocrine disruptors, the same toxicological outcome may be produced by a variety of different mechanisms. The bipyridilium herbicides, paraquat and diquat, may be considered to comprise a CMG in regard to their renal toxicity, but diquat does not share the lung toxicity of paraquat as diquat is not actively taken up into the lung as is paraquat. A scheme for assigning pesticides to CMGs on the basis of pesticidal action, structure/activity relationships, proprietary toxicological data and mechanistic studies has been described (2). How to cumulate: the step of assessing risk, based on data on the intake of all the pesticides in CMGs is done using methods that allow for the potency of the pesticides in the group relative to one another. This step is sometimes referred to as cumulation. There are a number of methods of cumulation (3) and no settled international consensus on which is the best method to use. The methods available are the Hazard Index (HI), the toxicity equivalence factor (TEF), the combined margin of exposure (MOE_T), the Point of Departure Index (PODI) and the Cumulative Risk Index (CRI) methods. All give similar but not identical results and may require CMG-specific reference doses and/or uncertainty factors. *Conclusion:* preliminary results from the United States and the United Kingdom, suggest that cumulative and aggregate risk assessment of OPs does not reveal unacceptable exposure to these pesticides. Work is on-going in several countries to define CMGs. It is anticipated that aggregate/cumulative risk assessment will be carried out in further groups of compounds in the future. *References:* 1. Cassee FR, Sühnel J, Groten JP, Feron VJ. In: Ballantyne B, Marrs TC, Syversen T (eds). General and Applied Toxicology. Macmillan: London, 2000, 303–320. 2. Fenner-Crisp PA. FQPA Science issues: common mechanism of toxicity and cumulative risk assessment. *Regul Toxicol Pharmacol* 2000; 31:308–310. 3. Wilkinson CF, Christoph GR, Julien E, Kelley JM, Kronenberg J, McCarthy J, Reiss R. Assessing the risks of exposure to multiple chemicals with a common mechanism of toxicity: how to cumulate? *Regul Toxicol Pharmacol* 2000; 31:30–43.

52. Pregnancy Outcome After Suicide Attempt by Drug Ingestion: A Nine Year Prospective Study

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Objective: To describe the fetal consequences of maternal drug self-poisoning during a nine year period (1995 to 2003). *Methods:* All pregnant women hospitalized in the emergency department or the intensive care unit of the regional hospital for suicide attempt by drugs were prospectively studied. Data collected included demographic data, medical history, clinical data and follow up. Data from new born examination were also recorded. *Results:* From 1995 to 2003, 194 pregnant women attempted suicide by drugs in 198 separate episodes (4 patients attempted suicide twice during the same pregnancy). Mean age was 25.8±6.4 years. Of these, 21 women had a medical history of depression, 9 of psychiatric disorders, 21 of previous self poisoning, 4 of drug abuse, 6 of alcohol abuse and 33 of tobacco smoking. No severity or mild severity was observed in most cases (n=187) and 5 poisonings were moderate and 2 were severe. No woman died of intoxication. Complete follow up was obtained for 121 patients (62%). Of these 121 evaluated pregnancy outcomes, 4 ended in spontaneous abortion, 10 in elective abortion, 3 in therapeutic pregnancy termination and 104 in live born infants. Focussing on the most vulnerable period for the fetus, 87 women attempted suicide during the first trimester after conception and 51 of them (59%) were followed up. Pregnancy outcomes were 4 spontaneous abortions, 10 elective abortions, 3 therapeutic pregnancy terminations and 34 live born infants. The characteristics of these 34 live born infants are: sex ratio male/female: 1.66, mean weight 3009 g±788 g, mean height 48.5±3.2 cm, mean cranial circumference 33.8±2.1 cm. Nine infants (26%) weighted less than 2500 g. Prematurity of birth (less than 38 weeks of amenorrhea (WA)) was documented for 6 live born infants (18%). Out of them, one was severe (less than 33 WA), 3 were moderate (33–35 WA), 2 were mild (36–37 WA). No malformations were observed within these 34 live born infants. *Conclusion:* This study supports earlier studies that reported that drug intoxication during the first trimester of conception does not seem to pose a substantial teratogenic risk but a tendency to an increase in the incidence of low birth weight and prematurity. However, continuation of this study is needed because of the small number of the sample and the difficulty in following up this population.

53. Drug Abuse in Early Pregnancy and the Risk of Fetal Loss

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Objective: To determine the use of drugs of abuse (DOAs) in high-risk early pregnancy and their effect on fetal loss. *Method:* 290 women were approached consecutively when first attending the Early Pregnancy Assessment Unit at St. Thomas' Hospital between October 1998 and January 1999. This is an emergency clinic for women between 6–18 weeks pregnant experiencing abdominal pain and/or vaginal bleeding. 256 (88%) women consented to participate in the study, which used a combination of an interview by questionnaire and urine analysis prior to a transvaginal ultrasound scan. Follow-up questionnaires were sent to participants' doctors. *Results:* There were 48 exclusions and the remaining 208 participants were divided into two groups—live births (117) and fetal loss (91). Fifty-three (25%) women had used a DOA. Cannabis had been used by 52 (25%) women, 18 (15%) with live births and 34 (37%) with fetal loss; this difference was significant (Odds Ratio [OR] 3.28, 95% CI 1.62–6.73). Nine women (4%) had also used cocaine and 1 (0.5%) amphetamine, no opioid abuse was found. During pregnancy, 59 (28%) women smoked. Women with fetal loss reported smoking more cigarettes per day (average 2.94, SD 4.91) than those with live births (average 1.40, SD 3.34, p=0.011) and had higher urine concentrations of nicotine metabolites (average log10 urine cotinine 1.74 (SD 1.1) compared to 1.29 (SD 0.92), p=0.002); for each cigarette per day, OR=1.10 (95% CI 1.02–1.18) and 10-fold increase in cotinine, OR=1.56 (95% CI 1.17–2.09). Cannabis use and smoking cigarettes (as measured by urine cotinine) were each predictive of fetal loss. If these were taken into account, every 10-year increase in age was also a significant predictor. Further analysis, adjusting for these three, showed that cannabis use increased the odds of fetal loss by 3.62 (95% CI 1.70–7.74), ten years of age by 2.10 (95% CI 1.25–3.55) and a tenfold increase in urine cotinine by 1.41 (95% CI 1.02–1.95). *Conclusion:* This study found a previously unreported association between cannabis use in early pregnancy and an increased risk of fetal loss. However it remains to be shown whether the strong association found here can be extended to the general pregnant population.

54. Outcome of Pregnancy Following Maternal Treatment with Proton Pump Inhibitors

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Objective: Gastrointestinal problems are common complaints of pregnancy and although many can be treated with dietary modifications, antacids or sucralfate, more severe or chronic conditions may require treatment with proton pump inhibitors (PPIs) (1–3). The objective of this prospective case series is to assess potential fetotoxicity following treatment of pregnant women with PPIs. *Method:* Using standardised procedures, NTIS has provided prospective fetal risk assessment and collected outcome data in 91 pregnancies exposed to therapeutic doses of PPIs. *Results:* The results are shown in Table 1. The majority (69/74) of liveborn babies were normal (93.2%). The incidence of malformations (5/74) was 6.8% vs. 2–3% expected. The malformations included two babies with talipes (one also had hydronephrosis which resolved spontaneously), and one baby with a bilateral hydrocoele, all exposed to lansoprazole plus other drugs. Of the 2 babies exposed to omeprazole monotherapy, one had a minor penile deformity and the other had an absent left middle finger. The incidence of miscarriage (8.6% vs. 10–20%) and elective terminations (11.8% vs. 23%) was within the expected range. Approximately 50% involved first trimester exposures and 2 mothers took a PPI throughout pregnancy. Where recorded, there were no significant differences in sex ratio and none of the singleton, term babies were small for dates (<2.5 Kg). *Conclusions:* The majority of liveborn babies were normal. The incidence of malformations in women treated with omeprazole and lansoprazole is higher (6.8% vs. 2–3%) than expected in the UK, but the small numbers preclude the drawing of reliable conclusions. However the malformation rate is in line with the overall malformation rate for high risk pregnancies (5.3%) recorded on the NTIS database. The data are confounded by some of the pregnancies being exposed to polytherapy. Further data are required before any firm conclusions can be drawn regarding the safety of PPIs in pregnancy. *References:* 1. Kallen B. *Br J Obstet Gynaecol* 1998; 105:877–881. 2. Lalkin A, et al. *Am J Obstet Gynecol* 1998; 179:727–730. 3. Ruigomez A, et al. *Am J Epidemiol* 1999; 150(5):476–481.

TABLE 1
Outcome of pregnancy following maternal treatment with PPIs

Exposures (n)	Liveborn normal	Liveborn malformation	Miscarriages	Elective termination
Omeprazole (44)	34*	2	3	5
Lanzoprazole (41)	29*	3	4#	5
Rabeprazole (3)	3	0	0	0
Pantoprazole (4)	3	0	1	0
Esomeprazole (1)	0	0	0	1~
All PPIs (93)	69*,@ (93.2%)	5 (6.8%)	8	11

*Includes one set of twins.
#One pregnancy exposed to omeprazole and lanzoprazole.
~Also exposed to omeprazole.
@7 with neonatal problems and 1 neonatal death (unrelated to PPIs).

55. Heroin, Methadone, and Buprenorphine Overdoses: Prospective Comparative Assessment of Conditions, Severity, and Treatment

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Objectives: High-dosage buprenorphine has been approved since 1996 as substitution treatment of heroin addiction. Despite a ''ceiling effect'' for respiratory depression (1), deaths have been attributed to buprenorphine intravenous misuse or sedative drug concomitant intake (2). Our objectives were to test whether buprenorphine pharmacological characteristics are

lost or not in the setting of overdose, in comparison with heroin and methadone. *Methods:* Prospective study including all consecutive patients admitted with mental status alteration and at least 2 of the 3 following criteria [a history suggestive of opiate/opioid poisoning, pinpoint pupils or respiration rate $\leq$12/min] and the exclusive presence of 6-monoacétylmorphine, buprenorphine or methadone. Institutional ethics committee of the French Critical Care Society approved the study. Results are expressed as median [25–75% percentiles]. Comparisons were performed using c2 and Kruskal-Wallis tests. *Results:* During a 4-year period (2000–2004), 160 patients were admitted in our 2 ICUs for acute severe opiate/opioids poisonings, allowing the inclusion of 84 patients (72M/12F, age: 36 years [32–42], Glasgow Coma Score: 6 [3–10], respiratory rate: 11/min [8–14], SpO_2: 90% [79–97]), with 26 in the ''heroin'' group, 39 in the ''buprenorphine'' group, and 19 in the ''methadone'' group. The most commonly associated sedative drugs were benzodiazepines (65%), ethanol (20%), phenothiazines (13%), meprobamate (10%), and phenobarbital (4%). Tetrahydrocannabinol and cocaine were present in 46% and 24% of the cases, respectively. Management included mechanical ventilation (44%), catecholamines (38%), naloxone (65%), and flumazenil (25%). One methadone-poisoned patient died from post-anoxic brain damage. Like heroin, buprenorphine poisoning was more significantly correlated to misuse than methadone which appeared linked to suicide attempt (p=0,0007). Psychotropic drug ingestion was always constant in buprenorphine overdoses (p=0,04). Buprenorphine was responsible of a significantly lower respiratory depression (SpO_2: 94% versus 82% and 91% for heroin or methadone, p=0,05) and a trend towards a deeper coma (Glasgow Coma Score: 7 [4–10] versus 5 [3–9] et 4 [3–10], p=0,1). Consistently, in accordance with buprenorphine pharmacological properties (1,3) and by opposite to reported observations (4), naloxone did not improve poisonings, contrasting with flumazenil effect when benzodiazepines were co-ingested. *Conclusions:* Buprenorphine overdose induces an opioid syndrome, with a trend towards less severe respiratory depression, however not reversed by naloxone. *References:* 1. Walsh SL. *Clin Pharmacol Ther* 1994; 55:569–580. 2. Pirany S. *Addiction* 2004; 99:978–988. 3. Gal TJ. *Clin Pharmacol Ther* 1989; 45:66–71. 4. Boyd J. *Acta Anaesthesiol Scand* 2003; 47:1031–1033.

56. Anaphylactoid Reactions to Intravenous Acetylcysteine, Frequency, Risk Factors and Outcome

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Objective: Paracetamol (acetaminophen) is involved in 35–45% of all episodes of drug overdose in the United Kingdom. Early administration of intravenous acetylcysteine is effective at preventing liver damage but use is restricted to patients at higher risk of paracetamol hepatotoxicity because it can cause dose-dependent histamine-mediated anaphylactoid reactions (AR) which are occasionally severe (1). These occur in 5–14% recipients (2–4) and may be more common in patients with atopy and in those with lower plasma paracetamol concentrations (2). The purpose of this research was to estimate the frequency of this adverse effect in a current UK population and to identify patient groups at increased risk. *Methods:* The computer records of all patients presenting to the Freeman Hospital with paracetamol poisoning between 2000 and 2003 were examined to identify patients who had received acetylcysteine and where clinical features suggesting an anaphylactoid reaction were recorded. *Results:* Of 1965 episodes of paracetamol overdose, 455 (23%) were treated with acetylcysteine and 18 (4%) of these were complicated by AR. Most cases were mild, with features restricted to the skin (flushing, urticaria, itching); only 3 had systemic features. In 14 cases acetylcysteine was re-instituted at a lower infusion rate, 12 received an antihistamine 6 hydrocortisone, and 2 nebulized salbutamol. All recovered without sequelae. Comparing affected with unaffected patients, there were no significant differences in the proportion of females (63% vs. 53%) or mean age (28 vs. 34 y). The proportions of patients at high, intermediate and low risk of paracetamol poisoning according to current nomograms were similar recipients with and without AR. However, patients with AR had lower mean paracetamol concentrations (81 vs. 130 mg/L) and were more likely to have been started on treatment more than 4 h after the overdose (83 vs. 37%, P=0.015). Atopy was present in 5 of 16 patients with an anaphylactoid reaction who had this information recorded, including 2 of the 3 with respiratory features. Two patients who had previously experienced AR were again treated with acetylcysteine following a further paracetamol overdose; one of these developed AR on the second occasion. *Conclusions:* Anaphylactoid reactions to acetylcysteine are common but usually mild. The data support the previously recognised association with atopy and the increased frequency in those with lower plasma paracetamol concentrations and/or those who present later. *References:* 1. Appelboam AV, et al. *Emerg Med J* 2002; 19:594–595. 2. Schmidt L, Dalhoff K. *Br J Clin Pharmacol* 2001; 51:87–91. 3. Yip L, et al. *Crit Care Med* 1998; 26:40–43. 4. Chan TY, Critchley JA. *Hum Exp. Toxicol* 1994; 13:542–544.

57. Hemodialysis for Acetaminophen-Induced Acute Liver Failure

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Objective: Acetaminophen (APAP) is now the leading cause of acute liver failure in the United States and the United Kingdom. Despite the use of the antidote N-Acetylcysteine (NAC), over one-fourth of these patients die, and only a small number survive long enough or qualify for liver transplantation. The subset of patients with severe metabolic acidosis has the worst prognosis for rapid deterioration and death, with a survival rate of <10%. *Case Series:* Six patients were admitted over a 16 month period to a regional poison treatment center in APAP-induced acute liver failure, with coagulopathy, encephalopathy, and metabolic acidosis. All 6 were late-presenting after acute (3) or chronic (3) APAP overdose. At admission 4 of the 6 met criteria for liver transplantation based on persistent acidemia (pH<7.30) after fluid resuscitation. All were treated with intravenous NAC and underwent emergency hemodialysis for 4–7 hrs. Data for admission pH, peak prothrombin time (PT), peak creatinine (Cr), peak grade (1–4) of hepatic encephalopathy (HE), pre-dialysis APAP elimination half-life (T $^1/_2$), and APAP half-life during dialysis (HD T $^1/_2$) are recorded in Table 1. All patients fully recovered without transplantation. *Conclusion:* Early hemodialysis may improve the outcome of APAP-induced acute liver failure with severe acidosis. Our data supports a need for further research into hemodialysis in the management of APAP-toxic patients qualifying for transplant.

TABLE 1
Clinical and kinetic parameters

	pH	PT (sec)	Cr (mg/dl)	HE	T $^1/_2$ (hrs)	HD T $^1/_2$ (hrs)
Mean	7.17	40.3	2.7	2.7	12.8	2.2
Range	7.01–7.38	18.7–60	1.2–6.7	1–4	7.9–30.1	1.6–2.8

58. Evidence and Consequences of Spectrum Bias in Studies of Criteria for Liver Transplant in Paracetamol Hepatotoxicity

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Objective: In severe paracetamol hepatotoxicity, orthotopic liver transplant (OLT) is a standard treatment in patients judged to have a hopeless prognosis. The most commonly used criteria to make this decision are the King's College Criteria (KCC) (O'Grady 1999). We aimed to compare the expected survival for patients who meet the KCC and do not receive transplant and those who receive OLT. *Methods:* A systematic review of studies of survival in patients who met the KCC according to whether they were transplanted. Data from these studies was extrapolated to compare long-term survival with and without adjustment for Quality of Life. *Results:* The survival of patients meeting KCC and undergoing transplant has not been specifically studied. UK data on transplants for acute liver failure indicate 1 and 10 year survival rates of 65% and 44% respectively. Survival in those not transplanted was documented in 9 studies. The average long-term survival rate was 26.5%. Survival was much worse in studies from the Kings College unit (12% vs. 48%). It was apparent that this may be due to spectrum bias in the studies reported from this much larger unit. There was clear evidence that those with the best prognosis were preferentially transplanted at the Kings liver unit, indicating the criteria may perform significantly worse at predicting death without transplant than previously estimated. Using the average survival rate of 26.5%, for a 20 year old with the KCC, the best estimate of mean life expectancy with transplant (13.8 years) is no better than without transplant (14.3 years). Adjustment for quality of life made OLT clearly a worse option. *Conclusion:* Criteria for OLT that have a much higher positive predictive value (for death without transplant) are required. Such studies must be conducted only on those who would be considered suitable for transplant. Non orthotopic liver transplant may be a preferred option in such circumstances, although much more data on survival after this procedure are required. *Reference:* O'Grady JG, Alexander GJ, Hayllar KM, Williams R. Early indicators of prognosis in fulminant hepatic failure. *Gastroenterology* 1989; 97:439–445.

59. Development of a New Pharmaceutical Product

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There are two stages in the life of any new chemical entity that eventually becomes a medicine: one involves invention, the other innovation. Invention is the discovery of a new drug or a novel potential use for an existing drug or chemical. Innovation involves meeting all the regulatory requirements to develop, manufacture and market a product that other people can use—and that they will buy! Invention or discovery is the relatively easy part of this process—almost everyone has a bright idea from time to time, but there is great amount of effort involved in making that idea become a reality. An early step is to ensure confidentiality—once an idea is in the public domain, it may be impossible to patent the concept, and it will then be very difficult to find sponsors. An agreement needs to be established with one's employing institution, and confidentiality agreements need to be signed with potential collaborators. Once confidentiality is secured, early work is required to prove the principle—this involves basic experimental work to ensure that the concept will work in practice. After this, the idea can be patented. The product will need to be manufactured in sufficient amounts to a satisfactory degree of purity for all of the preliminary experimental work, and this often requires a considerable investment. Then comes the first time that the substance is given to man—this will be an ascending dose study in healthy (male!) volunteers to ascertain the safety and basic pharmacokinetics of the substance. After this, studies of increasing size are needed to determine the effects and ensure the potential effectiveness of the product. At every stage, regulatory requirements need to be met. These will be considerably less if the new entity qualifies as an orphan drug, and this is likely to be the case for a new method of treating poisoning. At every stage of development, difficulties arise which need to be overcome. Examples of several of these steps will be given with reference to a new potential treatment for poisoning (alpha1 acid glycoprotein) which is currently under development.

60. Improving Antidote Development: A Business Perspective

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As clinical toxicologists we must accept that we have a dismal track record in bringing effective antidotes to market. In the past 40 years only a handful of new drugs have been approved in the US (DigiBind, CroFab, DigiFab, Antizol, NAC), with others available only on a compassionate use on named patient basis (coral snake antivenin, CPG-2, anti-scorpion antibodies). In Europe, the picture is similar. Although proven, safe and effective technologies exist (specific polyclonal antibodies; recombinant enzymes) few drugs are being developed. The process is long, and often fails although the drug itself maybe clearly effective. Why is this so? This presentation attempts to identify where we have gone wrong, and what we can do better. Key to any improvement is an appreciation of the role and motives of the three stakeholders—the investigator (the clinical toxicologist), the sponsor (usually a pharmaceutical company) and the regulator (national authority/EMEA). For the clinical toxicologist, regulatory trials present multiple hurdles. A scarcity of patients can make obtaining an adequate sample size highly unpredictable, and lack of a placebo control makes the burden of proof much harder. For the sponsor, a rare condition may make the cost of pursuing the project just too high when compared to other opportunities. For the evidence-based regulator, the compromises necessary for burden of proof as regards both efficacy (usually involving surrogate endpoints) and safety (size of material studied) maybe just be too uncomfortable when compared with the standards by which regulatory approval in controlled trials are justified. A better understanding of the ethical, political, and financial conflicts arising from the often opposing interests of these three stakeholders is essential if we are to improve our track record and collectively get effective antidotes more quickly to our patients.

61. Colchicine Antibodies—Experience and Problems of Development

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Objectives: Colchicine poisoning is rare in Western countries but responsible of a high-rate mortality. Colchicine toxicity is dose-dependent with multiorgan involvement and delayed onset. Mortality rate is strongly dependent on the ingested dose, around 90% when the ingested dose is above 0.8 mg/kg of body weight. Recognized prognostic factors include the supposed ingested dose, a decrease in prothrombin time rate $\leq 20\%$ (% of normal values), an elevation in white blood cell count $\geq 18 \times 109$/l in the 24 hours, and the onset of cardiogenic shock in the 72 hours following admission. Cardiac toxicity and negative inotropic effects

of high-doses of colchicine were largely assessed in experimental and human studies (1). Patients with early hemodynamic collapse due to colchicine overdose have particularly poor prognosis. To date, there is no successful commercially available specific therapy for colchicine intoxication, although several experimental studies and one human case report assessed the efficiency of colchicine-specific Fab fragments in this poisoning. The objectives of this presentation were to describe the requisites, hopes, and disappointments of colchicine Fab development in the past few years. *Methods:* Review of the international literature, including experimental and clinical studies. *Results:* Immunotoxicotherapy (ITT) is a procedure able to simultaneously sequester, extract or redistribute, and eliminate the toxin by using specific active binding sites derived from different antibody molecular entities (2). ITT is currently used in humans for treating cardiac glycoside and venom poisonings. Since the initial report in 1976 by Smith et al. of a digoxin intoxication reversal by an equimolar dose of digoxin-specific Fab fragments, ITT has become first-line treatment of life-threatening intoxication by cardiac glycosides, including digoxin, digitoxin, and other structurally related cardiotoxins from *Nerium*, *Thevetia sp.* (oleander), and *Bufo sp.* (toads). Colchicine is a good candidate for the development of a successful ITT, as it perfectly answers to the toxin-dependent requisite (3). Colchicine is responsible for severe poisonings with a high risk of death. Toxicity is in the milligram range. Colchicine efficiently produces an antibody response in animals, after conjugation to a protein. Colchicine distribution volume is much greater than its corresponding Fab fragment, with the possibility of a rapid redistribution from tissue to blood. However, other characteristics of colchicine poisoning may theoretically limit ITT potential benefits. Firstly, whereas cardiac glycosides are membrane-associated toxins, efficiently reversed with an equimolar dose of digoxin-specific Fab fragments, colchicine is low-molecular weight acting intra-cellularly poison, needing to consider an expanding ITT model to intracellular toxins. Secondly, by opposite to digitalis poisonings where only one organ, the heart, is at vital risk, severe colchicine poisonings induce multi-organ failure with not always reversible structural injuries. Therefore, in order to consider any therapeutic interest of colchicine-specific antibodies, it is necessary to hypothesize that ITT-associated neutralization of residual unbound colchicine may avert a lethal outcome, even if a greater part of the toxin has already damaged the organism. Colchicine neutralization with antibodies has proven to be effective in vitro and in animal studies. Although intracellular binding of colchicine to microtubules was expected to limit ITT efficacy, a reversible effect on microtubules was found in vitro. Colchicine-induced polyploidy and chromosomal aberrations in a model of Chinese hamster ovary cell were reversible with a specific high-affinity colchicine-binding monoclonal antibody, even when administered up to 6 hours after colchicine exposure (4). A tightly bound intracellular toxin was extracted with high-affinity antibodies at a rate depending on its dissociation rate from its receptors (5). Kinetics was characterized by a first-order decline with half-lives ranging from 15.5 to 16.4 h. Interestingly, anti-colchicine active immunization demonstrated protective effects in pre-immunized rabbits treated with 3-mg/kg colchicine, with an antibody titer-dependent response (2). In mice, colchicine-specific IgG administration, even after colchicine distribution phase, significantly decreased mortality rate (6). Colchicine-specific goat IgG (1/2 – 1/8 molar dose, administered 90 min after colchicine infusion) favorably improved outcome, when administered to mice previously receiving an intraperitoneal 3.8-mg/kg lethal dose of colchicine (7). Both IgG and Fab fragments altered colchicine pharmacokinetics, inducing a significant decrease in colchicine steady-state volume of distribution with its sequestration in the intravascular space and a decrease of its concentrations in most tissues of treated mice, indicating an ITT-mediated tissue extraction process (8). In rabbits, high-affinity goat colchicine-specific Fab fragments ($Ka = 1.1 \times 1010$ M-1) could sequestrate and extract colchicine from tissues to the vascular compartment with a subsequent colchicine excretion by the renal route (9). Colchicine-specific Fab fragments were infused 1.5 h after 0.1-mg/kg colchicine, over 0.25 h with at a 1/2-stoichiometrically equivalent dose. Within 15 min after Fab infusion, total colchicine concentrations increased 10- to 16-fold. The mean area under the plasma concentration-time curves increased 20-fold compared to controls. The free plasma fraction decreased to an undetectable level over a period of 2 h. During ITT, colchicine followed the elimination kinetics of the Fab fragments. ITT resulted in a 24- and 17-fold decrease of the distribution volume and total body clearance, respectively. A significant 80%-reduction of colchicine cumulative biliary excretion and a drastic reduction of colchicine dose fraction excreted by the urinary route (38% to 9%) were observed in Fab-treated animals in comparison to controls. Colchicine uptake by specific Fab fragments was confirmed in vitro in isolated hepatocytes, showing a reduction of colchicine biliary excretion despite no modification of the metabolic profile and suggesting a biliary formation rate-limited excretion of colchicine metabolites (10). The unique clinical use of anti-colchicine specific Fab fragments in human was reported in 1995, in a 25-year-old woman who ingested 0.96 mg/kg colchicine (11). Fab administration 36 hours after ingestion was associated with the reversal of cardiovascular failure, but did not prevent the delayed occurrence of bone marrow aplasia, complete hair loss, and transient peripheral neuropathy. Regarding toxicokinetics, Fab fragments administration increased the total plasma colchicine concentration (12 to 122 ng/ml), as soon as 10 minutes after the start of infusion, whereas the free colchicine concentration became undetectable. A 6-fold increase in colchicine urinary excretion was reported, initially bound to Fab fragments. To date, no commercial preparation of colchicine-specific Fab fragments is available. However, some requisites should be considered to develop such an antidote for human use (3). The tendency is to prepare polyclonal rather than monoclonal antibodies, based primarily on the industrial manufacturing capacity and to enlarge specificity to more epitopes. Another tendency is to prefer ovine rather than equine antibodies, in order to reduce serum sickness and as sheep tend to produce a higher proportion of specific IgGs per total IgGs in response to immunization. Consistently,

antibodies with high affinity (greater than 109 M-1, which represents a critical minimal value for efficient antibodies) are still awaited. Regarding the minimal efficient dose to administer, both animal and human reports showed that inframolar neutralization was efficient. They clearly confirmed that removal of even a modest portion of colchicine may dramatically improve outcome, challenging therefore the classical thinking of the necessity of a rapid administration of the total dose of Fab fragments to improve poisonings with ITT (12). Regarding therapeutic action, further studies are needed to determine the colchicine-specific Fab effect on bone marrow aplasia in poisonings. *Conclusions:* Coclchicine-specific Fab fragments may be useful to complete the supportive care in the most severe colchicine poisonings. However, to date, these fragments are still not commercially available. Until issues of cost and supply are worked out, coclchicine-specific Fab fragments may remain a dream in many of the areas where severe poisonings are frequent and specific therapy is urgently required. *References:* 1. Mery P. *Intensive Care Med* 1994; 20:119–123. 2. Scherrmann JM. *Toxicology* 1989; 56:213–222. 3. Bismuth C. *Hum Exp Toxicol* 1997; 16:602–608. 4. Rouan SE. *Am J Pathol* 1990 ; 137:779–787. 5. Chappey ON. *J Pharmacol Exp Ther* 1995; 274:1072–1076. 6. Terrien N. *Toxicol Appl Pharmacol* 1990; 104:504–510. 7. Sabouraud AE. *Toxicology* 1991; 68:121–132. 8. Sabouraud AE. *J Pharm Pharmacol* 1992; 44:1015–1019. 9. Sabouraud AE. *J Pharmacol Exp Ther* 1992; 260:1214–1219. 10. Sabouraud AE. *Drug Metab Dispos* 1993; 2:997–1002. 11. Baud FJ. *N Engl J Med* 1995; 332:642–645. 12. Baud FJ. *Arch Toxicol Suppl* 1997; 19:271–287.

62. Double-Blind Chemical Exposure Experiment in Patients with MCS

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Objective: Patients with Multiple Chemical Sensitivity (MCS) react to low levels o chemicals with symptoms in multiple organ systems. It is an acquired disorder, and symptoms can not be explained by known medical or psychiatric diseases. It is not clear whether the MCS responses are directly induced by chemical effects or whether they represent psychosomatic reactions triggered by olfactory perception, cognitions and emotions. To clarify this question we performed a double-blind exposure experiment in a challenge chamber. *Hypotheses:* 1. Patients with MCS are able to distinguish reliably between chemicals and placebo. 2. There are also significant differences in objective biological and neuropsychological parameters between chemical and placebo exposures. *Methods:* 20 patients with MCS and 17 control persons matched for age and gender participated in the experiment. Each subject underwent 6 consecutive 15 minute exposure sessions (3 solvent and 3 placebo, i.e. clean air, exposures in random order, double-blind), each followed by a 15 minute break. We used a mixture of 6 common solvents (toluene, xylene, ethylacetate, heptane, decane, undecane) in a concentration of about 800 $\mu g/m^3$ (below odour threshold). We performed continuous recording of the EEG as well as repeated monitoring of blood pressure, heart rate and cognitive performance speed, measured with the Zahlen-Verbindungs-Test (ZVT). Positive reactions were defined as 1. subjective perception of being exposed to solvents or 2. blood pressure and/or heart rate change of $\geq 10\%$, exanthema or hypoxia or 3. symptom severity rise to 3 or 4 on a 5-point scale after exposure. *Results:* Patients had a higher tendency to rate chemical exposure, whereas controls tended to rate placebo. More patients (30%) than control subjects (12%) showed ''correct'' reactions in more than 3 exposure sessions. More patients (30%) than controls (18%) reacted ''correctly'' with regard to blood pressure and heart rate. Both groups did not differ significantly for subjective exposure perception A symptom rise to 3 or 4 was not observed in the control group, and occurred only five times in the patient group. There was a tendency towards a higher proportion of patients with more correct reactions than false reactions, but the difference was not significant. Cognitive performance was not influenced by solvent exposure, and there were no significant differences between the groups. Our hypotheses could not be confirmed. *Discussion:* Significant group differences were not found. However, they could not be definitely excluded, because the power was not sufficient. Studies with sufficient power to exclude such differences would require much larger sample sizes that are hardly attainable under realistic conditions.

63. Clinical Trials in Sri Lanka: The Challenge and Opportunity

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Asia and other parts of the developing world bear a disproportionate burden of illness from acute and chronic toxicity. The current major problems of agrochemical self-poisoning and snake bite are responsible for more than 400,000 deaths per year. In

urban areas the emergence of pharmaceutical poisoning presents new challenges. This presents a major public health challenge and an opportunity for collaborative clinical toxicology research and training between European and Asian countries (1). Currently in Sri Lanka a clinical toxicology research program has been established funded predominately from competitive grants (Wellcome Trust and Australian NHMRC). This has allowed the establishment of research infrastructure which provides both a model and opportunity for collaborative research. There are funding opportunities that are available to EU members that specifically target collaborative work with partners in Asia. Current collection of clinical data and conduct of trials draws upon the intellectual and technical support of a number of institutions in Europe and Australia. Research is based upon the collection and maintenance of poisoning cohorts in 2 study hospitals situated in the agricultural area of North Central Province. These cohorts exist for both toxinology and toxicology and are based upon assayed confirmed exposure and repeated physical examination. They include more than 7000 patients and accrue a further 2000 patients each year. The poisoning cohort has facilitated the conduct of 2 large randomized clinical trials as well as some observational studies (2–4). Some results of this program will be presented in 4 papers in this meeting (RCT of superactivated charcoal, charcoal treatment compliance, relative toxicity of organophosphates, yellow oleander kinetics). These papers directly relate to other current research projects on the effects of pesticide restriction and the implementation of changes in clinical practice. Currently there is a large RCT of the WHO recommended regime for pralidoxime. SACTRC's current PhD program includes studies on cognitive impairment and electrophysiological studies of organophosphate poisoning, pharmacoeconomic assessment of treatments, the value of immunosuppressant treatments and the predictive value of prognostic tests in paraquat poisoning. The group has ethical approval for a number of phase 2 trials using diazepam or clonidine or magnesium in organophosphate poisoning. Barriers to research include cultural difference, ethics approval and logistics. The process of ethical approval has been refined over the past 3 years but is extensive and typically includes at least one overseas and one Sri Lankan university as well as the local institution. The logistics of import and export for drugs and samples have been established for 3 years and have facilitated collaborative work with international partners. The barriers are down, the current funding creates a window of opportunity for clinical toxicology which we should grab now and develop into a sustainable global program of activity. *References:* 1. Buckley NA, Karalliedde L, Dawson A, Senanayake N, Eddleston M. Where is the evidence for treatments used in pesticide poisoning? Is clinical toxicology fiddling while the developing world burns? *J Toxicol Clin Toxicol* 2004; 42(1):113–116. 2. Eddleston M, Rajapakshe M, Roberts D, et al. Severe propanil [N-(3,4-dichlorophenyl) propanamide] pesticide self-poisoning. *J Toxicol Clin Toxicol* 2002; 40(7):847–854. 3. Roberts DM, Karunarathna A, Buckley NA, Manuweera G, Sheriff MH, Eddleston M. Influence of pesticide regulation on acute poisoning deaths in Sri Lanka. *Bull World Health Organ* 2003; 81(11):789–798. 4. Buckley NA, Roberts D, Eddleston M. Overcoming apathy in research on organophosphate poisoning. *BMJ* 2004; 329(7476):1231–1233.

64. Adverse Reactions to Intravenous Acetylcysteine: Effects of Reducing the Infusion Rate of the Loading Dose

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Objective: Intravenous acetylcysteine is usually regarded as a safe antidote. However, during the infusion of the loading dose adverse drug reactions (ADR) including flushing, headache, nausea, vomiting, angioedema, skin rush, hypotension, and bronchospasm may occur. It has been suggested that these anaphylactoid effects could be related to the drug infusion rate. Therefore, we investigated the incidence of ADR to acetylcysteine after administration of the initial bolus over a longer time period. *Methods:* A prospective, observational study was performed over a 6-months period. All patients treated with intravenous acetylcysteine were included. Medical and toxicological history were obtained. Patients were given acetylcysteine 150 mg/kg over 90 minutes (1.7 micrograms/kg/minute). ADR ensuing within 180 minutes after the onset of the loading dose were recorded. *Results:* Among 42 eligible patients, 2 cases were excluded because of incomplete data. Forty patients were eventually studied, who received acetylcysteine because of suspected acetaminophen (23/40, 57.5%), halogenated hydrocarbons (13/40, 32.5%), or other (4/40, 10%) poisoning. Medical history documented asthma in 1 patient; medications, co-ingestants, and/or therapy given in the Emergency Department before acetylcysteine administration included antihistamines in 4 patients, and nonsteroidal anti-inflammatory drugs and/or steroids in 9 cases. ADR were observed in one patient only (1/40, 2.5%); in patients without confounding factors (such as medications that could mitigate or prevent acetylcysteine side effects) ADR rate was 3.7% (1/27). The observed reaction was mild (skin flushing), did not require specific therapy, and did not modify antidote administration regimen. *Conclusion:* According to standard protocols, acetylcysteine loading dose is usually administered over

15 to 30 minutes (10 to 5 micrograms/kg/minute). In retrospective studies such infusion rates are associated with ADR in 5.3 to 11% of patients, up to 48.4–56.0% in prospective case series. ADR incidence is 3 times greater in asthmatic patients. Two prospective studies (1,2) documented that reducing the infusion rate from 15 to 60 minutes decreases ADR incidence from 56.0% to 19.6% of patients. The results of this study confirm the above mentioned clinical observations and suggest that a further decrease of the speed of initial bolus is associated with further reductions in ADR. *References:* 1. Donovan JW, Jarvie D, Prescott LF, et al. Adverse reactions of N-acetylcysteine and relation to plasma levels. *Vet Hum Toxicol* 1987; 29:470. 2. Donovan JW, Corayeb MJ, Kulig KW, et al. Adverse reactions to slow infusion of intravenous N-acetylcysteine. *Vet Hum Toxicol* 1990; 32:347.

65. Mortality Rate in Amatoxin Poisoning with Different Antidotal Treatments

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Objective: A retrospective study was undertaken to find out the influence of different so-called antidotal treatments for *amanita* poisoning. Two groups of patients with amatoxin intoxication were recruited. Firstly a mono-centre evaluation from our treatment centre (Munich) including 274 patients was done. Secondly 315 cases from a post-marketing surveillance by the Madaus firm in patients receiving silibinin in different hospitals and countries were studied. Antidotal treatment and mortality was looked at in both groups. *Material:* Patients from the Munich subgroup: From 1957 till 1970 78 cases were treated with no antidote. From 1970–1980 43 patients were treated with penicillin only, from 1980–1993 108 cases were treated with silibinin plus penicillin. From 1997–2003 45 cases were treated with silibinin only. One patient from the silibinin plus penicillin group and 4 patients from the silibinin only group underwent liver transplantation (LTx). Patients from the Madaus subgroup: 204 patients were treated with silibinin+penicillin or/and cephalosporins. 111 cases were treated just with silibinin. *Results:* The result of the Munich patients are given in Table 1. The results from the Madaus cases in Table 2. *Conclusion:* Taking only the results from Munich into consideration, no improvement no matter what ''antidotes'' have been used could be found. The

TABLE 1
Munich patients

Time and treatment	Total number	Number of death	% Mortality
1957–1970—no antidote	78	5	6,41
1971–1980—penicillin only	43	3	7,14
1981–1993—penicillin+silibinin	108	14 (1 LTx)	12,96 (13,88)
1994–2003—silibinin only	45	4 (4 LTx)	8,89 (17,77)

TABLE 2
Madaus patients

Treatment	Total number	Number of death	% Mortality
Silibinin+penicillin or/and cephalosporins	204	17	8,33
Silibinin alone—all without LTx	111	0 (!)	0

Madaus post-marketing surveillance study points to a 100% improvement if silibinin is used alone. Treatment with a combination of antidotes with silibinin has the same mortality rate as the Munich group. We suspect a reporting bias in the Madaus surveillance because no patient with LTx shows up there. Possibly these cases were not reported because no one felt responsible to report them after successful transplantation.

66. What Trials Should We Now Do on N-Acetylcysteine?

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The paucity of clinical trials in poisoned patients has hampered the development of clinical toxicology. Clinical trials are difficult to perform for reasons that include the heterologous nature of acute poisoning, the infrequency of adverse clinical outcomes and ethical difficulties in obtaining consent from patients whose mental capacity may be clouded by the substances they have taken or their underlying psychiatric disease. Paracetamol (acetaminophen) poisoning is a common problem, with 35–45% of all overdose presentations or 58,000 episodes each year involving this drug in England and Wales, 5,500 of which are sufficiently severe to require antidotal treatment on current criteria (1). Effective antidotes for paracetamol are oral methionine (2) and intravenous (3) or oral (4) n-acetylcysteine. In the UK intravenous n-acetylcysteine is standard treatment. Although effective, there are unanswered questions in terms of efficacy, adverse effects and convenience of use. *Efficacy:* The evidence for benefit from intravenous n-acetylcysteine was derived from a case series of high risk patients treated with the antidote, comparing outcomes with those of historic controls (3). The dose and infusion schedule, chosen pragmatically, was so effective in reducing the incidence of severe hepatotoxicity that randomized controlled clinical trials have never been required to demonstrate benefit in this patient group. Nevertheless, a few patients still develop hepatotoxicity in spite of n-acetylcysteine treatment and more effective regimens would be valuable. In patients presenting early, comparative trials with alternative regimens such as methionine or oral acetylcysteine would have to be very large indeed to demonstrate reductions in rates of adverse clinical outcomes such as fulminant hepatic failure, requirement for liver transplantation and/or death, because these are so uncommon with intravenous n-acetylcysteine. Use of surrogate endpoints indicating hepatic dysfunction (e.g. prothrombin time, hepatic transaminases) would reduce the numbers of patients required for adequate study power but probably not by enough to make such trials practical. Evidence for benefit from acetylcysteine administered more than 15 h after poisoning is currently lacking; even with antidotal treatment the risk of clinically important hepatic dysfunction is sufficiently large that it may be possible to perform a placebo-controlled clinical trial with adequate power to demonstrate clinically important improvement in efficacy compared with placebo. However, small trials have suggested survival benefit in patients with established fulminant hepatic failure (5) and clinicians may not be content to use a placebo under these circumstances. There is less certainty about the benefit of antidotes in patients at lower risk and it is worth considering a clinical trial in patients whose risk of hepatotoxicity is considered borderline. Liver dysfunction develops in about 20% untreated patients with paracetamol concentrations between the 100 and 200 mg/L treatment lines (3) and about 260 patients would need to be randomised to each group to demonstrate a reduction to 10% with antidote (alpha=0.1, Beta=0.05). *Adverse Effects:* Up to 17% of recipients develop an anaphylactoid reaction to n-acetylcysteine resulting from a dose-related increase in plasma histamine concentration. Although rarely severe and easily controlled by reducing the infusion rate and administration of antihistamines, these reactions are one reason for limiting use of the antidote to patients at higher risk. Altered infusion schedules that reduce the risk of this effect without reducing efficacy would make the use of intravenous n-acetylcysteine more attractive in patients at lower risk of hepatotoxicity. It is possible to perform clinical trials to demonstrate whether these reduce the rates of anaphylactoid reactions, although one small study has not established benefit from reducing the initial infusion rate. Almost 400 patients would be needed in each group to demonstrate a reduction from 15 to 7.5%. It would be more difficult to establish whether such regimens were at least as effective in preventing hepatotoxicity. *Cost of Therapy:* The duration of treatment required means that many patients need to stay in hospital for more than one night and there would be advantages to having a shorter infusion schedule. Clinical trials would have to demonstrate that this was as effective as the original schedule and was no more toxic. Large patient numbers would be required, e.g. about 6,000 in each group to exclude an increase from 3% to 4% in incidence of severe liver dysfunction after treatment. *Conclusions:* Paracetamol poisoning is sufficient common that clinical trials are potentially feasible but these would have to be large and a multi-centre approach is required. In the first instance, pilot studies to test recruitment methods and establish the frequency of proposed endpoints would be appropriate. *References:* 1. Thomas SHL, et al. *Hum Exper Toxicol* 1997; 16:495–500. 2. 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67. Developing Evidence—Molecular Adsorbents Recirculating System (MARS) as a Critical Example

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Introduction: MARS is a new elimination technique developed since 15 years for the treatment of acute hepatic failure (AHF) (1). Compared to the other elimination techniques, MARS has the capacity to remove albumine-bound toxins and that may be responsible for the beneficial effects observed in AHF (1–4). Therefore, it has been suggested that MARS may be usefull in poisoned patients for the removal of drugs with a high protein binding. *The MARS Technique:* Developed in the 1990s, the technique combines kidney dialysis (the selective removal of substances normally cleared by the kidneys) with liver dialysis (the selective removal of substances normaly removed by the liver). The simultaneous selective extraction of both water-soluble and albumine-bound toxins is based on conventional renal replacement therapy and albumine dialysis. The specific properties of the MARS membrane (an albumine-impregnated high-flux polysulfone membrane) ensure the elimination of these toxins. Another key feature is the use of human serum albumine as toxin acceptor in the dialysate. The dialysate is then regenerated by passing through three different elimination devices: a haemodiafilter to remove water-soluble toxins and then an activated charcoal and an anion exchange resin column to remove albumine-bound toxins. Substances with a molecular weight (MW) higher than 50 kDa are not removed (1–4). *The Potential Indications:* In poisoned patients, MARS may have two different indications: the treatment of severe poison induced AHF and the use as an enhanced elimination technique. MARS has been evaluated in various causes of liver failure and seems to improve circulatory failure, renal dysfonction, intracranial hypertension and encephalopathy. Therefore, this technique may serve as a bridge to liver transplantation, when indicated, or may allow to overcome the critical period of hepatic failure until liver regeneration has occurred (2–4). Randomized controlled trials are under way in order to evaluate the adequate indications and the end-points. MARS has been used in the treatment of ALF due to *Amanita* and paracetamol poisoning (5–8). No conclusions can be made given the limited number of cases and because the criteria for indication were not clearly defined. Some reports have shown that MARS may increase the elimination of drugs such as midazolam, fentanyl, diazepam, fluoroquinolones, and several other antibiotics (9). MARS has been used in one case of phenytoin poisoning (10). The analytical data showed that phenytoin was eliminated by the MARS system, especially, by the choarcal and resin haemofilters. However, despite a decrease in phenytoin serum levels, the usefulness was not established because no calculations of the elimination clearances and of the amounts removed were made. *Methodology for the Evaluation of MARS in Poisonings:* The choice of the poisons should be based on physicochemical criteria (MW, protein binding, water- and lipid solubility, blood flow rate, dialysate flow rate, adsorptive capacity of haemofilters), kinetic criteria (low volume of distribution, low total body clearance) and dynamic criteria (life-threatening poisonings with no efficient antidotal or supportive treatment). The kinetic evaluation should not only be based on the decrease of the poisons serum concentrations, but should include the clearances and the amounts of the poisons removed by the 4 systems: MARS dialyser, haemodialyser, activated charcoal filter and polymer filter. The amounts of poisons removed must be compared with the spontaneous elimination. Moreover, the evaluation has to include the effects on morbidity and mortality of the enhanced poison elimination. *Conclusion:* MARS is a new elimination technique which may have some indications in poisonings. However, its potential use has to be evaluated by a precise methodology including kinetic and dynamic criteria in order to avoid many errors made in the past with other elimination techniques. In poisoned patients, the indications of MARS for treatment of AHF and for enhancing the poison elimination should be clearly determinated. Because MARS is an expensive technique, its evaluation is mandatory. *References:*
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Davies NA, et al. Treatment of phenytoin toxicity by the molecular adsorbents recirculating system (MARS). *Epilepsia* 2003; 44:265–267.

68. Clinical Trials in Refractory Cardiogenic Shock

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In Europe, the incidence and prevalence of cardiogenic shock (CS) due to acute poisonings remains unknown. In the USA, a 4.9% increase of poisonings had been reported between 2001 and 2002 (1). Circulatory insufficiency is one of the major causes of death in acute poisonings. The global mortality rate of poisonings is low (about 1%). However, it remains higher for cardiotropic drug intoxications such as class I and IV antiarrhythmics (about 10%). In 2002, in the USA, the first class of drugs involved in fatalities (1153 cases) was analgesics and sedative/hypnotic/antipsychotic agents. The second class of drugs primarily responsible for death was polycyclic antidepressants (318 cases), principally amitriptyline. One of the most common life-threatening events induced by polycyclic antidepressants poisoning is its membrane stabilizing effect. Cardiovascular agents were the fourth cause of death (181 deaths) after psychostimulants and street drugs. Excluding experimental and in vitro studies, some clinical trials have assessed the refractoriness of CS in cardiac diseases principally for acute coronary syndrome. Refractory CS during acute coronary syndrome is clinically defined as a systolic blood pressure that progressively deteriorated to lower than 100 mm Hg despite maximal percutaneous revascularization, intra aortic balloon pump and intra-venous dopamine (at least 7 microg/kg/min), furosemide, and fluid treatment for at least one hour, accompanied by signs of peripheral hypoperfusion (2). To our best knowledge, there is no clinical and precise relevant definition of refractory shock in other acute cardiomyopathies. Whether the pathophysiological definition of irreversible shock—the terminal stage of shock—is the irreversible impairment of the cellular machinery leading to the cellular death, this definition cannot be used in clinical practice. Thus, several clinical case series defined the refractory CS as a shock unresponsive to conventional therapies including inotropic agents. However, there is no consensus and clear thresholds regarding the doses of dobutamine or epinephrine in the definition of this refractoriness. Drug-induced CS is a recognized cause of death. However, while the term of refractory CS is commonly used in toxicological textbooks, its definition has not been clarified. The pathophysiology of the refractory CS is not univocal. It may involve a severe diminution of inotropism, like with beta-blockers or membrane stabilizing agents (MSA) responsible for the inhibition of the fast sodium channel currents. CS may also be caused by arrhythmias and abnormalities of cardiac conduction, related for instance to digitalis poisoning. However, digoxin-specific Fab fragments are the treatment of life-threatening events. Thus, digitalis-induced CS due to ventricular arrhythmias is particularly observed in the case of lack of Fab fragment availability. Interestingly, the prognostic factors of life-threatening events for digitalis poisoning considerably simplified the indication of the antidote (3). We recently proposed clear cut-offs for the definition of refractory CS restricted however to acute MSA poisonings. This refractoriness should be evocated after maximizing and optimizing conventional treatment (mechanical ventilation, 8.4% bicarbonates, adequate fluid repletion, inotropes and/or vasopressors depending on the pulmonary artery catheter profile, glucagon for beta blockers intoxications. . .). We found the mandatory requirement of epinephrine at a dose more than 3 mg/h to maintain systolic blood pressure upper than 90 mm Hg despite conventional therapies. Criteria witnessing poor tissue perfusion were also mandatory to separate survivors from fatalities. These criteria include either renal failure as defined by anuria and an increase in serum creatinine above 120 mmol/l or severe hypoxemia (PaO_2/FiO_2 ratio lower than 150 mm Hg). In our experience, the low PaO_2 denotes the extremely low cardiac output in these patients with SvO_2 less than 45%. Validation of these criteria is associated with fatal outcome with a sensitivity rate of 87% and a specificity rate of 97% (4). Pre-existing cardiomyopathy could also be helpful in treatment algorithm for some authors. This refractory CS definition is not validated for calcium channel blockers intoxication including verapamil. In calcium antagonist poisonings, treatment includes euglycemic high dose insulin, calcium salts and high doses of vasopressors (5). Few clinical case series—more than clinical trials—have assessed the refractoriness of CS dealing with colchicine, theophylline or other cardiotoxic drug poisonings. It is noteworthy that the prognostic factors of cardiotropic drugs have been poorly investigated. Similarly, the prognostic value of the measurement of blood concentration of the toxicants in acute poisonings remained to be determined. We recently presented preliminary data suggesting that the measurement of plasma flecaine concentration on admission may be a prognostic value in acute flecaine poisoning (6). Recent therapeutic trials in refractory CS due to cardiac diseases have pointed out the possible efficiency of L-Name (a NO synthase inhibitor) or the interest of levosimendan (as new and more efficient inotropic agent). Vasopressin is actually tested comparatively to epinephrine in the treatment of cardiac arrest. These treatments are not fully tested for refractory CS without cardiac arrest. The utility of glucose-insulin therapy for acute myocardial infarction with shock remains controversial (7). The usefulness of intra-aortic balloon counterpulsion is now documented for acute coronary syndrome but debated in its

precise indications and modalities. Necessity of angioplasty, urgent coronary artery bypass or other surgery is still associated with high mortality in coronary artery syndrome with CS (8). Temporary mechanical ventricular or circulatory assistance remains in these indications a bridge to bridge or a bridge to transplant alternative but the level of proof is low. More recently in acute poisonings, therapeutic case series focus on the efficiency of such temporary methods (5). Limits for intra-aortic balloon counterpulsion are its inefficiency when arterial pressure is lower than 40 mm Hg or in case of severe arrhythmias, electromechanical dissociation and cardiac arrest. Extra corporeal life oxygenation (ECLS) seems the most promising device in the treatment of refractory CS before occurrence of fatal outcome. ECLS is an arterio-venous method providing circulatory support but requiring bypass of blood from the right to left system. In this condition of ECLS, the addition of extra-corporeal membrane oxygenation is mandatory (ECMO is a veno-venous method improving PaO_2 without providing any support of the circulatory system). Peripheral circulatory assist devices are particularly useful when compared with more invasive methods such as conventional bypass support by sternotomy because management of refractory acute poisonings requires a simple method available for most centers and because these intoxications can reverse in a couple of days. To our knowledge, 28 cases reports of acute poisoning treated by such a method are documented. Only one team published a series of 6 consecutive cases (9). In 2002 in USA, ECLS therapy was provided in 8 cases in response to human exposures. Unpublished data in our unit and a previous review reports a 70% favorable outcome when ECLS is provided in MSA poisonings meeting the criteria of refractoriness (10). In conclusion, difficulty to evaluate precisely incidence or prevalence of refractory CS due to acute poisonings is due to the absence of quantitative definition. When CS is suspected consecutively to cardiotoxic agents intoxication, new guidelines as previously defined should be used to prevent a fatal outcome. Thus, in the absence of contraindication, ECLS should be considered as a promising method. *References:* 1. Watson WA, Litovitz TL, Rodgers GC, et al. 2002 Annual Report of the American Association of Poison Control Centers Toxic Exposure Surveillance System. *Am J Emerg Med* 2003; 21:353–421. 2. Cotter G, Kaluski E, Milo O, et al. LINCS: L-NAME (a NO synthase inhibitor) In the treatment of refractory Cardiogenic Shock. A prospective randomized study. *Eur Heart J* 2003; 24:1287–1295. 3. Hickey AR, Wenger TL, Carpenter VP, et al. Digoxin immune Fab therapy in the management of digitalis intoxication: safety and efficacy results of an observational study. *J Am Coll Cardiol* 1991; 17:590–598. 4. Megarbane B, Andujar P, Delahaye A, et al. Acute poisonings with membrane stabilising agents: analysis of the predictive parameters of non-responsiveness to conventional therapies. European Association of Poisons Centers and Clinical Toxicologists. *J Toxicol Clin Toxicol* 2003; 41:553–554. 5. Albertson TE, Dawson A, de Latorre F, et al. TOX-ACLS: toxicologic-oriented advanced cardiac life support. *Ann Emerg Med* 2001; 37:S78–S90. 6. Megarbane B, Delhotal B, Tchir M, et al. Toxicokinetic—toxicodynamic relationships in case of flecainide poisonings. European Association of Poisons Centers and Clinical Toxicologists. *J Toxicol Clin Toxicol* 2004; 42:477–478. 7. Hochman JA, Sleeper LA, Webb JG, et al for the SHOCK Investigators. Early revascularization in acute myocardial infarction complicated by cardiogenic shock. *N Engl J Med* 1999; 341:625–634. 8. The CREATE-ECLA randomized controlled trial. Effect of glucose-insulin-potassium infusion on mortality in patients with acute ST-segment elevation myocardial infarction. *JAMA* 2005; 293:437–446. 9. Batabasi G, Massetti M, Verrier V, et al. Severe intoxication with cardiotoxic drugs: value of emergency percutaneous cardiocirculatory assistance. *Arch Mal Coeur* 2001; 94:1386–1392. 10. Baud FJ, Guerrier G, Megarbane B, et al. Prospective assessment of clinical criteria of refractoriness to medical treatment in poisonings with membrane stabilising agents. European Association of Poisons Centers and Clinical Toxicologists. *J Toxicol Clin Toxicol* 2004; 42:473–474.

69. Randomised Controlled Trial of Routine Single or Multiple Dose Superactivated Charcoal for Self-Poisoning in a Region with High Mortality

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Background: in the rural developing world, case fatality from intentional self-poisoning is 10 to 50-fold higher than in the West, mostly due to the common use in these regions of highly toxic pesticides. In industrialised countries, routine use of activated charcoal is not recommended since there is no evidence for clinical benefit and few deaths that could be prevented by its use. We aimed to determine whether routine single or multiple dose regimens of superactivated charcoal offer clinical benefit in a region with high case fatality from self-poisoning. *Methods:* we set up an open randomised controlled trial of a single 50 g dose of superactivated charcoal vs six doses at four hour intervals vs no charcoal in March 2002 in three Sri Lankan hospitals, with death as the primary outcome. The trial was stopped in October 2004 at the third interim analysis after the target number of patients

had been recruited. *Results:* at this point, 4216 patients had been randomised to receive no charcoal (1405), a single dose of charcoal (1410), and six doses of charcoal (1401). Baseline characteristics were similar. 954 had ingested organophosphorus (OP) or carbamate pesticides; 1515 had ingested yellow oleander seeds. Overall, there was no difference in case fatality between patients who received multiple doses (87/1401) and those who received no charcoal (95/1405; odds ratio 0.91, 95% CI 0.67–1.25), and between patients receiving either regimen of charcoal (186/2811) and those receiving no charcoal (95/1405; OR 0.98, 0.75–1.28). There was no significant difference for patients ingesting any particular poison or for any time interval between ingestion and start of treatment. *Conclusions:* we found no evidence of benefit from the routine administration of superactivated charcoal for any form of acute poisoning in Sri Lanka; multiple doses did not seem to offer benefit over a single dose.

70. Observational Versus Interventional Studies in Clinical Toxicology: Hard Lessons Learned from Investigations on the Clinical Benefits and Adverse Effects of Hormone Replacement Therapy

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Controlled studies are the foundation upon which conclusions concerning the toxicologic effects of therapies are evaluated. However, simply being controlled does not confer immunity from methodologic flaws, subtle biases, and confounding factors. Thus, both the nature and design of controlled clinical studies must be considered in any critical evaluation of the reported results. Controlled clinical studies in toxicology can be either observational or interventional. The former are studies in which the effect of a treatment or exposure is correlated with specific endpoints. No attempt is made in these kinds of studies to provide any intervention determining which of the subjects is exposed. Thus these studies make passive observations on exposed and non-exposed populations. In contrast, interventional trials actively assign subjects into treated (or exposed) and control groups. A well-designed randomized double-blinded controlled clinical trial generally represents the gold standard for assessing clinical effects. Because the subjects are treated or exposed simply based on a randomization procedure the effects of bias or confounding are minimized. Thus, interventional trials, if appropriately designed and executed, produce a greater degree of certainty then do observational studies. Studies on the effects of hormone replacement therapy (HRT) in postmenopausal women provide a unique and poignant opportunity to compare the kinds of results obtained from observational studies with those of interventional trials. Because rates of cardiovascular disease rise after menopause or bilateral oophorectomy, the theoretical benefits to women of HRT have been the subject of numerous observational studies. The largest and best designed of these was the Nurses Health Study, which followed 121,700 nurses, aged 30–55, who were enrolled in a prospective study starting in 1976. The Nurses Health Study included careful verification of medical diagnoses and nearly complete follow up. An often cited 1985 publication from this study (1) reported on 32,317 post-menopausal women without prior heart disease followed up for an average of 3.5 years (105,786 person years). The use of estrogens was associated with a decrease in mortality (relative risk [RR] 0.5; confidence interval [CI] 0.3–0.8) and a statistically significant decreased risk of myocardial infarction or coronary heart disease events. A subsequent META analysis (2) evaluated six hospital-based case control, seven population-based case control, three cross sectional, and sixteen prospective studies. Thirty-one of these thirty-two were observational; one was a small interventional trial. Of these thirty-one observational studies, two showed no effects, four showed adverse cardiovascular effects (all non-statistically significant) and twenty-five showed a decreased cardiovascular risk; twelve of the latter being statistically significant. A weighting factor was developed that was proportional to the precision, or the inverse of the variance, of these studies and when applied to the universe of these data a treatment related RR of 0.56 (CI 0.5–0.61) for coronary heart disease was calculated. Largely based on these observational studies HRT was deemed a seemingly prudent approach to the primary and secondary prevention of coronary heart disease-related events and hence became a common practice. An apocryphal discussion by Barrett-Conner in 1991 noted that life style factors influence cardiovascular disease incidence rates and thus the apparent benefit of HRT may simply represent a surrogate for pro health-related behavior. If true, this would introduce considerable bias and confounding in the observational studies. Thus, in what retrospectively proved to be an insightful observation Barrett-Conner observed, in the face of almost overwhelming results from observational studies supporting HRT, ''despite considerable current enthusiasm for estrogen-replacement therapy as a panacea, only a randomized clinical trial can adequately address these biases and resolve this question.'' (3). Largely following the observational studies, there have been a number of randomized, placebo-controlled, double-blinded interventional trials on HRT, the most significant of which were the Women's Health Initiative (WHI) and the Heart and Estrogen-progesterone Replacement Study (HERS). The WHI enrolled 161,809 post-menopausal women aged 50–79 between 1993 and 1998. A number of clinical trials were included in WHI including two on post-menopausal hormone use. The two HRT arms of the WHI were an estrogen plus progestin regimen for women with a uterus and estrogen alone for women post hysterectomy, each with placebo controlled parallel groups. The estrogen plus progestin arm

of the WHI was prematurely terminated in 2002 because of concerns about breast cancer and cardiovascular endpoints. In this study there was a non-significant increased risk (hazard ratio [HR] of 1.26) for invasive breast cancer, a significant time trend for developing breast cancer, and a borderline risk of achieving one of several cardiovascular disease endpoints combined (HR 1.22; CI 1–1.49) (4). HERS was a randomized blinded placebo controlled interventional trial of 2,763 post-menopausal women with known cardiac disease. Women in HERS were randomized to conjugated estrogens plus a progesterone or placebo (5). In 1998 the HERS study reported an apparent increase in risk of primary coronary events in the first year of therapy. (Relative hazard [RH] 1.52, CI 1.01–2.29) There was no statistically significant risk or benefit with therapy related to this endpoint after one year. There was a treatment-related significant time trend of decreasing fatal myocardial infarction over time and a significant improvement in lipid profiles. The RH of venous thromboembolic disease was 2.69 (CI 1.50–5.58), with no significant time-related trend. (5) Because this elevated RH for primary coronary events was only seen early, women were continued on HRT for up to 6.8 years of observation. The original intention was to continue the study further but at the second annual data review it was felt that it should be terminated. The reported results of continued therapy (HERS II) were that there was no beneficial effect of continued HRT, although no adverse effects were documented. (6). A META analysis (7) of the WHI, HERS, and a third trial known as the Women's Estrogen for Stroke Trial, found significant increases in relative risk of stroke (RR 1.3, CI 1.1–1.5), pulmonary embolism (RR 2.16, CI 1.47–3.18), and breast cancer (RR 1.24, CI 1.03–1.56). Relative protection was reported for colorectal carcinoma (RR 0.64, CI 0.45–0.92), endometrial carcinoma (RR 0.76, CI 0.45–0.92), and femoral neck fracture (RR 0.72, CI 0.52–0.98). There was no significant trend for coronary heart disease endpoints. The precise reasons for the conflict between the risk documented in interventional trials and apparent benefit reported in the observational studies is yet to be fully elucidated. However one major hypothesis is that in the observational trials an uncontrolled bias towards more healthful behavior in women taking HRT may have been responsible for their fewer adverse events. Such a confounder should not be present in the randomized interventional trials. Thus while the role of observational studies in clinical toxicology cannot be minimized, it must be recognized that they may also be vulnerable to confounding and bias. Consideration of these factors is therefore obligatory before conclusions can be drawn from their results. In contrast, as the HRT studies dramatically demonstrate, well-designed and properly executed placebo-controlled blinded interventional trials tend to minimize biases. In the case of HRT markedly contradictory results were obtained by these two kinds of studies indicating the limitation of purely observational studies and the importance of interventional clinical trials for assessing toxicologic effects (1). Stampfer MJ, Willett WC, Colditz GA, et al. A prospective study of postmenopausal estrogen therapy and cardiovascular heart disease. *N Engl J Med* 1985; 313:1044–1049. 2. Stampfer MJ, Colditz GA. Estrogen replacement therapy and coronary heart disease: a quantitative assessment of the epidemiologic evidence. *Int J Epidemiol* 2004; 33:445–453. (Published as a reprint of this article which was originally published in 1991). 3. Barrett-Conner E: Postmenopausal estrogen and prevention bias. *Ann Int Med* 1991; 115:455–456. 4. Women's Health Initiative Investigators: Risk and benefits of estrogen plus progestin in healthy postmenopausal women. Principal results from the WHI Randomized Controlled Trial. *J Am Med Assoc* 2002; 288:321–333. 5. Hulley S, Grady D, Bush T, et al. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. *J Am Med Assoc* 1998; 280:605–613. 6. Grady D, Herrington D, Bittner V, et al: Cardiovascular disease outcomes during 6.8 years of hormone therapy. *J Am Med Assoc* 2002; 288:49–57. 7. Beral V, Banks E, Reeves G. Evidence from randomized trials on the long-term effects of hormone replacement therapy. *Lancet* 2002; 360:942–946.

71. Prospectively Measured Compliance for Single and Multiple Dose Regimens of Superactivated Charcoal in Self-Poisoning Patients

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Objective: Prospectively measure compliance for single and multiple dose regimens of superactivated charcoal in self-poisoning patients. *Method:* 691 patients with a history of acute self-poisoning presenting to Polonnaruwa general hospital and Kurunegala teaching hospital, Sri Lanka between the 29th October 2002 and 31st December 2003 in Polonnaruwa, and from 23 November 2002 until 31st January 2003 in Kurunegala, were enrolled on admission in a RCT of treatment with single and multiple (six doses q4h) 50 g doses of superactivated charcoal (Carbomix, Norit, NL). Demographic, exposure and outcome data were recorded prospectively. Charcoal was given by study doctors who recorded the amount ingested

(Estimates were made to the nearest 25%) and the amount of persuasion required for the patients to drink the charcoal (semi-quantitated as 'none,' 'little,' or 'lots'). *Results:* 355 patients were randomized to receive one dose and 336 to receive six doses. Data was available for 669 (97%) patients. Fifty one were not able to complete their course; 64 required a nasogastric tube, leaving 554 patients that received the first dose by mouth. The mean estimated amount of charcoal ingested as a single or first dose was 80%. For patients receiving multiple doses, this amount fell over the next five doses to 61%. The mean amount of charcoal that was ingested after the first dose fell to 72%, 68%, 66%, 63% and 61% for the 2nd, 3rd, 4th, 5th and 6th doses, respectively. While only 2% of patients refused the first dose, 15% refused the sixth. Relatively little persuasion was required for patients ingesting the first dose; 39% of patients required intense persuasion by the sixth dose. *Conclusion:* Compliance for a single dose of superactivated charcoal among trial patients was good. However, even in the ideal

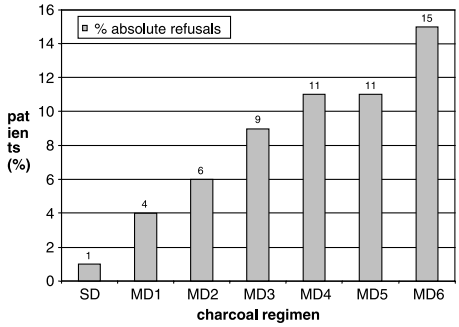

FIG. 1. Number of patients refusing each dose of charcoal.

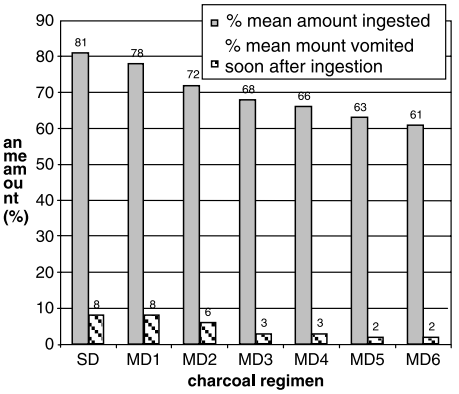

FIG. 2. Estimated mean proportion of each dose of activated charcoal ingested and vomited straight after.

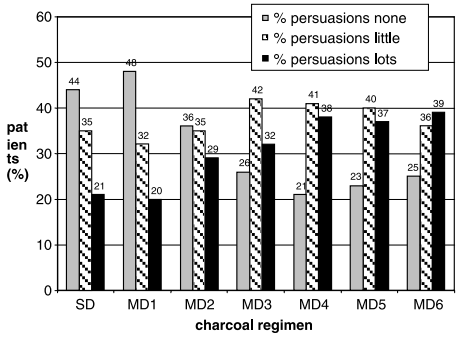

FIG. 3. Degree of persuasion used for each dose of charcoal.

circumstances of a RCT, compliance decreased thereafter for patients taking more than one dose. Extrapolation of human volunteer charcoal studies to the clinical situation will always be hindered by poor compliance. *References:* 1. de Silva HA, Fonseka MMD, Pathmeswaran A, et al. Multiple-dose activated charcoal for treatment of yellow oleander poisoning: a single-blind, randomised, placebo-controlled trial. *Lancet* 2003; 361:1935–1938. 2. American Academy of Clinical Toxicology and European Association of Poison Centres and Clinical Toxicologists. Position statement: single-dose activated charcoal. *J Toxicol Clin Toxicol* 1997; 35:721–741.

72. Glucarpidase (Voraxaze™), a New Methotrexate Antidote Drug: Clinical Development from an Industrial Standpoint

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Methotrexate serum concentrations can remain elevated in patients with renal insufficiency after they have been treated with high doses (greater than 1 g/m^2). This is a rare complication of cancer treatment with a chemotherapeutic agent but can lead to death. Glucarpidase, (Carboxypeptidase G2, Voraxaze™) is a recombinant enzyme that upon infusion clears greater than 95% of serum methotrexate in fewer than fifteen minutes by cleavage to a non-toxic metabolite. Clearance of the drug from the serum reduces the potential for further toxicity (Widemann et al, 2004). Patients treated early with Glucarpidase (within 4 days or less of initiation of methotrexate) show improvements in key clinical parameters including less severe (grade 3/4) neutropenia in 45% of treated patients compared to 73% in patients treated late ($p<0.0002$); reduced damage to the gastrointestinal lining with high grade stomatitis observed in only 22% of patients treated early compared to 65% in those treated late ($p<0.0001$) and fewer methotrexate related deaths, 3% in patients treated early compared with 28% in those not receiving Glucarpidase until 5 days or more after methotrexate initiation ($p<0.0001$). In clinical trials only 5% of patients have experienced adverse effects possibly related to Glucarpidase and no serious adverse events or deaths have been observed. The impact of the rarity and unpredictable occurrence of this condition on the conduct of clinical studies of Glucarpidase under both European and American regulatory guidance, and the importance of supply worldwide by named patient sales and compassionate use protocols in North America will be discussed. Finally, the availability of an antidote to the potential life threatening side effects of methotrexate gives the potential for changing clinical practice with high dose methotrexate. The long term implications of this will also be discussed. *Reference:* Widemann BC, et al. *Cancer* 2004; 100:2222–2232.

73. Organophosphate Induced Delayed Polyneuropathy (OPIDP): Clinical and Mechanistic Aspects

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Exposures to certain organophosphorus esters (OPs) may cause a rare toxicity known as OPIDP. These OPs include various insecticides and some non-anticholinesterase triaryl phosphates, used as plasticizers and hydraulic fluids. OPIDP is characterized by a symmetric distal sensory-motor central-peripheral axonopathy that affects the legs and, in most severe cases, also the arms. Pre-marketing dose-effect studies in animals select OP insecticides with higher cholinergic toxicity, relatively to their capability to cause OPIDP. Thus, in the case of exposures to insecticides, neuropathy develops exclusively after severe cholinergic toxicity. However some authors suggested that peripheral nerve dysfunction may be a consequence of low-level repeated exposures to OP insecticides and/or nerve agents, such as those that occurred during the Gulf War in soldiers and during sheep dipping in british farmers. Careful reviews of epidemiological clinical and mechanistic evidence do not support the notion that low-level exposures to these OPs caused peripheral neuropathy (Lotti, 2002). *Clinical:* Symptoms and signs of OPIDP begin 2–3 weeks after single doses, whereas, the onset is more variable and less definable after repeated exposures. OPIDP is fully expressed within a few days of the onset and no progression has been observed in the absence of further exposure. The usual initial complaint is cramping muscle pain in the legs, followed by distal numbness and paresthesia. Progressive leg weakness may occur together with depression of tendon reflexes. Signs include a characteristic high-stepping gait associated with bilateral foot drop. Severe OPIDP may result in flaccid quadriplegia with pyramidal signs. In time there is a complete functional recovery if spinal cord axons have been spared by smaller doses. Otherwise, pyramidal and other signs of central neurological involvement may become clinically more evident and spastic ataxia may represent a permanent outcome of severe OPIDP. Objective evidence of sensory loss is usually slight or absent. The electrophysiological changes accords well

with the histopathological findings of a distal axonopathy and parallels clinical signs of peripheral neuropathy (Moretto and Lotti, 1998). *Mechanistic:* The mechanism of OPIDP initiation is thought to involve the phosphorylation of a neuronal protein with esterase activity known as Neuropathy Target Esterase (NTE) (Johnson, 1990). OPs causing OPIDP react covalently with NTE at its catalytic centre, acting as pseudo-substrates. Whereas the rate of hydrolysis of phosphorylated NTE is extremely slow, NTE becomes virtually permanently inhibited. The phopshorylated enzyme can subsequently undergo a second reaction, known as aging, which results in the loss of one of the bound OPs alkyl groups. This two step mechanism, occurring within hours after poisoning, is thought to initiate OPIDP. However, other OPs such as organophosphinates may also react covalently with NTE but cannot undergo the aging reaction. As a consequence, these OPs do not cause OPIDP and when given to experimental animals before a neuropathic OP, they protect from OPIDP. This mechanism suggests that either neuropathic OPs cause a loss of a non-enzymatic function of NTE, or that NTE has no essential role, and placing a negative charge at its active site induces a toxic gain of function (Glynn, 1999). Recent studies with the recombinant domain of NTE suggest that membrane lipids are the putative cellular substrates of this enzyme, raising the possibility that NTE may be involved in intraneuronal membrane trafficking (van Tienhoven et al., 2002). *References:* Glynn P. *Biochem J* 1999; 344:625–631. Johnson MK. *Toxicol Appl Pharmacol* 1990; 1:385–399. Lotti M. *Muscle and Nerve* 2002; 25:492–504. Moretto A, Lotti M. J. *Neurol Neurosurg Psychiatr* 1998; 64:463–468. Van Tienhoven M, Atkins J, Li Y, Glynn P. *J Biol Chem* 2002; 277:20942–20948.

74. The Role of Atropine and Oximes in the Treatment of Organophosphorus Insecticide Poisoning

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Background: The number of intoxications with organophosphorus pesticides (OPs) is estimated at 3 million per year, with some 200,000 deaths worldwide. OPs act primarily by inhibiting acetylcholinesterase (AChE) through phosphorylation of the active-site serine. Thereby acetylcholine accumulates at cholinergic synapses and disturbs transmission at parasympathetic nerve endings, sympathetic ganglia, neuromuscular endplates and certain CNS regions. *Features:* The live-threatening muscarinic symptoms include bronchorrhea, bronchoconstriction, bradycardia, and hypotension. The most dangerous CNS symptoms are coma and respiratory depression. These features may be counteracted with cholinolytics which, however, are ineffective at the nicotine-sensitive receptors at muscle endplates, leading to progressive muscle weakness of diaphragm and respiratory muscles. *Role of Atropine:* Atropine represents the cornerstone in the treatment of OP poisoning by competitively counteracting acetylcholine at m-receptors and antagonizing excessive bronchosecretion and bronchoconstriction. Atropine is less effective in counteracting convulsions which respond favourably to diazepam 10–20 mg IV. Recommendations on the atropine regimen in adults vary widely. The most efficient way to atropinize the patient both quickly and safely is to inject an initial IV bolus of 1–2 mg with subsequent doses doubled every 5 min until atropinization is achieved: clearing lungs, increasing heart rate to just 80–100 bpm, and reducing profuse sweating (''dry axillae''). With this regimen patients will be usually atropinized within 20 min. Thereafter, atropine may be given by continuous infusion. Excess atropine should be avoided, because of hyperthermia, confusion and agitation. In patients with coronary artery disease atropine-induced tachycardia may precipitate myocardial infarction. *Role of Oximes:* Pralidoxime and obidoxime are able to reactivate phosphorylated, non-aged AChE, thereby reducing the acetylcholine concentration and hence the cholinergic crisis. While these effects have been conclusively demonstrated in experimental settings the general clinical benefit in OP poisoning is not clear yet. There are several reasons for the contradictive reports: 1) The type of poison and particularly the dose are often unknown and may vary widely. 2) The extent of decontamination, induced by spontaneous vomiting, gastric lavage and activated charcoal, may greatly differ. 3) The regimen of oxime administration may vary, including the time having elapsed between ingestion of poison and oxime administration, oxime plasma concentration, and duration of oxime therapy. 4) Patients may differ with respect to enzyme polymorphisms in toxifying phosphorothioates (CYP superfamily) and hydrolytic detoxication (PON1). All these variables will markedly influence the balance between reactivation and re-inhibition by residing poison. Personal studies: We have performed an open, not randomised, not controlled multi-centre clinical study to follow the effects of obidoxime in severe OP poisoning. A comprehensive monitoring was elaborated to assess the cholinesterase status, the plasma concentrations of the OPs as well as the concentrations of obidoxime and atropine. The neuromuscular transmission was investigated by recording the compound muscle action potential of M. abductor digiti minimi after repetitive stimulation of the N. ulnaris. All patients received primary care by emergency physicians, including oxygen and atropine administration. The effectiveness of obidoxime was evaluated in 34 severely OP intoxicated patients (inclusion criteria: need for artificial ventilation) treated with a 250 mg IV obidoxime bolus,

followed by continuous infusion of 750 mg/24 h. The infusion was maintained as long as reactivation was possible. *Results:* 34 patients were treated for 65±53 h with 2.4±1.7 g obidoxime. Seven patients died on about day 20 (8–38 d) after intoxication. Five patients died because of severe aspiration of the oil- and solvent-containing vehicle leading to ARDS and sepsis (3 parathion, 1 oxydemeton-methyl, 1 phoxim), most of these patients needed resuscitation at the spot. One patient died immediately before being discharged as cured because of pulmonary embolism; one died because of penetrating gastric ulcer followed by overt peritonitis. This study shows that most case fatalities resulted from complications of the poisoning before medical attention and before atropine and oximes could be given. With the obidoxime regimen used, the targeted effective plasma concentration of about 10–20 micromol/L could be adjusted. Obidoxime was able to reactivate AChE, if the poison load was not too high and ageing was not complete. Moreover, it turned out that neuromuscular function was markedly improved when red blood cell (RBC)-AChE exceeded 15% of normal and was hardly impaired above 25%. This situation could frequently be achieved with OPs of the diethyl type, but rarely in dimethyl OP poisoning. In turn, intoxications with the dimethyl compounds were hardly so precipitous as observed with parathion. The mechanism behind the somewhat retarded intoxication is most probably the considerable spontaneous reactivation of dimethylated AChE (half-life 0.7 h), allowing some percent active AChE during the first hours even in the absence of oxime. Obidoxime was well tolerated and severe hepatotoxic effects were not observed. Transient pathological liver findings usually normalized when obidoxime administration was still ongoing. The atropine demand of patients with reactivated RBC-AChE was generally low. When the high plasma concentration from the bolus had disappeared steady state concentrations at about 10 nmol/L were usually found as long as RBC-AChE was above 10% of normal. This concentration was attained by <0.5 mg atropine/h. An additional observation deserves separate comment. A proper judgement of the effectiveness of oxime therapy in OP poisoning is hampered as the load of the absorbed poison is usually unknown. In 7 of our parathion poisoned patients we analysed the cumulative p-nitrophenol excretion. It turned out that the amounts absorbed were generally much lower than anticipated from anecdotal reports of relatives. *Conclusions:* The results of our obidoxime study show that effective reactivation can be expected primarily with the diethyl OPs. In this group, obidoxime and pralidoxime in appropriate doses should be administered as long as persisting poison is to be expected. In mega-dose poisoning and/or when the toxicant is slowly eliminated, oximes will not be able to prevent ageing. Oximes are less effective in dimethyl OP poisoning. RBC-AChE determination appears to be a reliable surrogate parameter for quantitative assessment of oxime effectiveness; its determination near the ward should be propagated.

75. What Can We Learn from the Management of OP Insecticide Poisoning to Optimize Treatment for Nerve Agent Poisoning?

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Background: Effectiveness of antidote therapy in nerve agent poisoning cannot be assessed in human beings for ethical reasons. Clinical course of poisoning by organophosphate (OP) pesticides follows the same principles as by nerve agents. Accordingly, it appeared rational to follow antidote effects as close as possible in OP pesticide-poisoned patients and assess, whether the findings correspond to those derived from experimental studies, thus allowing rational extrapolation to nerve agent poisoning. *Methods:* In a clinical trial, obidoxime was administered to severely OP-poisoned patients in addition to atropine as early as possible and as long as reactivatability of acetylcholinesterase (AChE) was anticipated. Red blood cell (RBC)-AChE activity, reactivatability of patient's RBC-AChE (incubation of diluted patient's RBCs with 100 μmol/l obidoxime in vitro), plasma level of obidoxime, and neuromuscular transmission were monitored. The data were compared with results derived from reactivation experiments on phrenic-diaphragm preparations of mice as well as human RBC-AChE exposed to various OPs and various oximes. From these results a strategy for oxime treatment and monitoring of nerve agent poisoning was derived. Furthermore, atropine amounts used were registered as well as its pharmacokinetics during poisoning and correlated with the cholinesterase status of the patients. *Results:* In OP-poisoned patients, inhibited non-aged RBC-AChE could be reactivated by obidoxime concentrations found to be effective in experimental studies. The degree of reactivation achieved in the patients correlated well with theoretical values, derived from calculations basing on plasma levels of obidoxime, paraoxon, RBC-AChE activity in vivo and reactivatability of patient RBC-AChE. Reactivation (RBC-AChE) and improvement of neuromuscular function in the patients correlated well and, when RBC-AChE activity exceeded some 30% of normal, neuromuscular transmission was hardly impaired. Comparably, in phrenic-diaphragm preparations paraoxon-induced neuromuscular failure was antagonized by oximes, when an increase of muscle AChE activity exceeding roughly 40% of normal was achieved. This close correlation of

neuromuscular function and AChE activity of muscle and RBCs point to RBC-AChE as a suitable surrogate parameter. Accordingly, effectiveness of oximes in nerve agent poisoning may be predicted from in vitro studies with human RBC-AChE, thus preventing from misinterpretations due to species differences of AChE. Studies conducted with nerve agents and human RBC-AChE revealed that the experimental compound HLö 7 appears to be the most appropriate reactivator (broadest spectrum, best reactivation properties), followed by HI 6, which also is not yet licensed and available on the common market. Generally, from the commercially available oximes obidoxime appears to be superior to pralidoxime in poisoning by most nerve agents and OP pesticides, especially when used at doses recommended in the product information sheets. *Conclusion:* Therapeutic benefit of oximes, namely reduced need of artificial ventilation in a mass casualty situation, may be anticipated when effective doses are administered early and long enough. Due to fast aging of some nerve agents (e.g. soman), oxime therapy has to be initiated as early as possible, at best by administration of autoinjectors by first aid personnel (e.g. fire brigades) when first signs and symptoms arise. Since during a terrorist attack or on a battlefield intoxication is expected to evolve mostly from small amounts of poison, e.g. rarely exceeding 2–5 times LD50, compared to megadoses used in suicide poisoning, a single i.m. oxime injection may be sufficient. However, several nerve agents that do not show fast aging may be released after absorption over a longer time from the tissue (e.g. VX) requiring oxime therapy over a longer period. In such cases oximes should be administered by infusion. To assess the timeframe over which oxime treatment is necessary a simple test system could be helpful. To this end reactivatability of RBC-AChE as well as inhibitory activity of patients plasma could be used. Oxime therapy should be maintained 1) as long as inhibited RBC-AChE is reactivatable. This can be tested in vitro by incubation of patient's plasma with HI 6 (100 μmol/l, 30 min incubation time, 37°C) resulting in reactivation. 2) Oxime therapy should be maintained as long as inhibitory activity is present in the plasma. Weaning from artificial ventilation should be taken into account when RBC-AChE activity is higher than 30% of normal, indicating unimpaired neuromuscular transmission. Neuromuscular transmission can be assessed by repetitive stimulation of the ulnaris nerve and recording the muscle compound action potentials at the hypothenar. Generally, huge amounts of atropine are not necessary, but dosing should follow a protocol warranting an early sufficient atropinization e.g. by using a starting dose of 2 mg i.v. followed by an observation period of 5 min. If there is no effect, this dose may be doubled every 5 minutes until muscarinic symptoms relieve. If no reactivation can be achieved atropine infusion at a rate $\leq$2 mg/h may maintain sufficient atropinization.

76. Are There Long-Term Sequelae from a Single Acute Organophosphorus Insecticide Exposure?

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Background: This review will examine the possibility that chronic effects, other than organophosphorus insecticide (OP)-induced delayed polyneuropathy, can occur after acute and symptomatic exposure to OP insecticides. Since acute intoxication with OPs can cause major effects such as convulsions, respiratory failure and cardiac arrhythmias, all of which can result in cerebral anoxia, it would be surprising if severe acute OP poisoning was not associated with long-term neurological sequelae. Moreover, there is now experimental evidence that such complications can occur (1). *Review:* Eight epidemiological studies (2–9) are relevant. Rosenstock et al. (2) and McConnell et al (3) investigated the neurophysiological effects (2) and, as an index of delayed neuropathy, measured vibrotactile thesholds (3) in 36 male agricultural workers in Nicaragua who had been admitted to hospital between 10 and 34 months earlier with occupationally-related acute OP poisoning; 21 of 36 workers had been poisoned with methamidophos, a recognized peripheral neurotoxin. In a battery of neuropsychological tests the exposed group performed significantly worse than the control group 2 and a significant decrease in vibrotactile sensitivity was also observed (3). Steenland et al. (4) studied 128 men exposed to OPs, the majority occupationally, who had sought medical attention and of whom 28% had been admitted to hospital in California for more than one night. The study group was divided into two sub-groups: ''probable'' cases (45/128) who had symptoms following OP exposure but in whom cholinesterase activity was not measured and ''definite'' cases (83/128) that had both symptoms and a red cell or plasma cholinesterase activity $\leq$20%. Neurobehavioural tests, nerve conduction tests and vibrotactile threshold responses were undertaken several years after exposure. The study group performed significantly worse in tests of sustained visual attention and mood and those in the ''definitely'' poisoned sub-group also showed significantly worse vibrotactile sensitivity of finger and toe, but had no neurological symptoms. Savage et al. (5) investigated the presence of chronic neurological or neuropsychological abnormalities in 100 subjects who had experienced at least one episode of acute OP poisoning confirmed by a physician. The authors found significant deficits in a wide range of neuropsychological variables, including visuomotor, attention and language function. Persistent abnormalities in affective behaviour, especially anxiety, were also found, though no differences on EEG or

neurological examination were identified. Miranda et al. (6–9) studied a cohort of men who were exposed predominantly occupationally to an OP insecticide and who had been admitted for at least one day to two hospitals in Nicaragua for treatment of OP poisoning. Data on AChE activity were available only in some 38% of exposed individuals and in 28% of controls. Quantitative tactile vibration thresholds were measured in 56 subjects on the first occasion 1–24 days (median 7) after exposure and for the second time 24–128 days (median 50) after poisoning and compared to 39 non-exposed men (6). The study group had their symptoms classified as mild (n=0), moderate (n=35) or severe (n=21). Big-toe vibrotactile thresholds increased markedly from the first to the second examinations in those with severe intentional poisoning (ingestion) due to neuropathic OPs (metamidophos, chlorpyrifos). No significant impairment of vibrotactile thresholds was detected in association with occupational poisonings or with less severe intentional poisonings with neuropathic or non-neuropathic OPs. In a further study (7) of the same population (n=59), marked impairment of grip and pinch strength in the dominant hand was found, particularly among those with severe poisoning due either to neuropathic OPs or intentional ingestion. In a third study (8) of the same exposed population, hand strength and vibration thresholds were performed in 48 men two years after admission for acute OP poisoning. In those exposed to non-neuropathic OPs, grip and strength had recovered and was not different from controls; pinch strength remained lower than for controls. Among those poisoned with neuropathic OPs, those who suffered only moderate poisoning showed an evolution similar to those exposed to non-neuropathic OPs, whereas those severely poisoned (notably as a result of intentional ingestion) still remained significantly weaker than controls. Index finger and toe vibration thresholds were slightly increased at the end of the two year period. In a fourth study (9) of the same population (n=53), changes in immediate verbal memory, visuomotor performance and neuropsychiatric symptoms at the time of discharge, seven weeks post-poisoning and at two years were evaluated. Immediate verbal learning showed deficits in the high exposure group, particularly at the time of discharge. Visuomotor performance showed a deficit at seven weeks but improved thereafter. A two year delayed excess of neuropsychiatric symptoms was present in those occupationally exposed. The authors concluded that visuomotor performance and possibly short-term verbal memory were affected early after severe acute OP poisoning and recover, either truly or by some compensatory mechanism. Neuropsychiatric symptoms seemed to increase after a longer latency period, particularly in the less severely exposed subjects. *Conclusion:* Despite some shortcomings in methodology, there is evidence from these studies that severe acute OP poisoning can produce subclinical damage to the central and peripheral nervous systems. *References:* 1. Sánchez-Santed F, Canadas F, Flores P, Lopez-Grancha M, Cardona D. Long-term functional neurotoxicity of paraoxon and chlorpyrifos: behavioural and pharmacological evidence. *Neurotoxicol Teratol* 2004; 26:305–317. 2. Rosenstock L, Keifer M, Daniell WE, McConnell R, Claypoole K, Pesticide Health Effects Study Group. Chronic central nervous system effects of acute organophosphate pesticide intoxication. *Lancet* 1991; 338:223–227. 3. McConnell R, Keifer M, Rosenstock L. Elevated quantitative vibrotactile threshold among workers previously poisoned with methamidophos and other organophosphate pesticides. *Am J Ind Med* 1994; 25:325–334. 4. Steenland K, Jenkins B, Ames RG, O'Malley M, Chrislip D, Russo J. Chronic neurological sequelae to organophosphate pesticide poisoning. *Am J Public Health* 1994; 84:731–736. 5. Savage EP, Keefe TJ, Mounce LM, Heaton RK, Lewis JA, Burcar PJ. Chronic neurological sequelae of acute organophosphate pesticide poisoning. *Arch Environ Health* 1988; 43:38–45. 6. Miranda J, McConnell R, Delgado E, et al. Tactile vibration thresholds after acute poisonings with organophosphate insecticides. *Int J Occup Environ Health* 2002; 8:212–219. 7. Miranda J, Lundberg I, McConnell R, et al. Onset of grip- and pinch-strength impairment after acute poisonings with organophosphate insecticides. *Int J Occup Environ Health* 2002; 8:19–26. 8. Miranda J, McConnell R, Wesseling C, et al. Muscular strength and vibration thresholds during two years after acute poisoning with organophosphate insecticides. *Occup Environ Med* 2004; 61:e4. 9. Delgado E, McConnell R, Miranda J, et al. Central nervous system effects of acute organophosphate poisoning in a two-year follow-up. *Scand J Work Environ Health* 2004; 30:362–370.

77. Is Toxicity Associated with Exposure to ''Low Dose'' Organophosphorus Insecticides?

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Background: Organophosphorus compounds have been widely used as insecticides in agriculture for over 50 years. Their acute toxicity in man is due to their anti-cholinesterase activity, and the severity of acute toxicity in man is also dependent upon the speed with which ''ageing'' of cholinesterase occurs. Over the past two decades there has been increased concern that exposure to insecticides in this group is associated with features which are not directly related to acute toxicity, and arise at exposure levels which do not cause acute symptoms. *Definitions:* A key issue in considering this topic is therefore a definition of ''low dose'' within the context of both workplace exposure, and exposure in other population groups. It is, therefore, clear that clinical poisoning, with features of cholinesterase inhibition may be followed by clinical sequelae. In defining ''low dose'' such patients

must be excluded. Since patients who believe they may have suffered symptoms following exposure are not seen acutely, actual evidence of exposure levels based on laboratory assay, or acute clinical assessment are generally unavailable. The majority of research in this area is therefore based on a combination of self reporting, with its obvious potential for confounding, or epidemiological studies in which potentially exposed groups of workers are compared to occupational ''controls,'' often in a different industrial environment. Other approaches use estimated extent of exposure based on specific occupational description and duration. Such an approach does not generally account for ''one off'' accidental exposure to higher concentrations due to, for example, contact with concentrate. *Workplace Factors:* Pesticide regulation includes an assessment of worker exposure, though this assumes best-practice, large safety margins are built in. Within the UK this issue was complicated by a legal requirement for farmers to dip sheep, and within the USA by a large numbers of agricultural workers being immigrant and potentially not being able to read warning labels. Working conditions and exposure loads vary in different working environments, in part because of the volatility of solvents and the practicality of wearing protective clothing in hot environments. Thus engineering controls had been encouraged within the agriculture industry, but these may also confound epidemiological studies. The majority of work in this area has been done on two worker groups, fruit sprayers in California and sheep farmers in the UK. The agents used in the two different industries are different, as our processes of application and frequency. Some researchers have postulated that specific patient groups may be at increased risk due to polymorphism in drug metabolising enzymes, or cholinesterase (Lockridge and Masson, 2000). Such hypotheses have also been tested in epidemiological studies, particularly with respect to paraoxonase (Cherry et al., 2002). The issue has also clouded by comparison to other syndromes of unclear origin (e.g. ''Gulf war'' syndrome). The majority of published research has involved an epidemiological approach and has concentrated on neuropsychological adverse effects. These have ranged from studies on EEG alone, tests of neuropsychological performance including reaction time and other neurobehavioural tests, nerve conduction studies and EMG up and up (Ray, 1998) Some evidence exists that knowledge about chemical action may affect response (Markowitz et al., 1986). A larger UK study on sheep dippers showed exposure to concentrate was an important hazard (Buchanan et al., 2001) but although groups could be differentiated based on clinical symptomatology this bore only a weak relationship to history of exposure to pesticides, which was heavily influenced by a small group of workers with potentially excess exposure (Pilkington et al., 2001). Suggestions of effects on the immune system are even more difficult to sustain. *Summary:* Organophosphorus pesticides are potentially toxic, but taken overall present evidence does not suggest biological effects in man that can conclusively be related to exposures that do not produce overt clinical signs of toxicity. *References:* Buchanan D, et al. Estimation of cumulative exposure to organophosphate sheep dips in a study of chronic neurological health effects among United Kingdom sheep dippers. *Occup Environ Med* 2001; 58:694–701. Cherry N, et al. Paraoxonase (PON1) polymorphisms in farmers attributing ill health to sheep dip. *Lancet* 2002; 359:763–764. Lockridge O, Masson P. Pesticides and susceptible populations: people with butyrylcholinesterase genetic variants may be at risk. *Neurotoxicol* 2000; 21:113–126. Markowitz JS, Gutterman EM, Link BG. Self-reported physical and psychological effects following a malathion pesticide incident. *J Occup Med* 1986; 28:377–383. Pilkington A, et al. An epidemiological study of the relations between exposure to organophosphate pesticides and indices of chronic peripheral neuropathy and neuropsychological abnormalities in sheep farmers and dippers. *Occup Environ Med* 2001; 58:702–710. Ray D. Organophosphorus esters: an evaluation of chronic neurotoxic effects. MRC Institute for Environment and Health, 1998.

78. Relative Clinical Toxicity of Organophosphorus Compounds

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Background: Organophosphorus (OP) pesticide self-poisoning causes around 200,000 deaths each year in the Asia Pacific region alone, with a case fatality (CF) often >10%. Textbooks treat OP poisoning as a homogeneous entity, differentiating OPs only by their animal toxicity using the WHO's Classification of Toxicity and, more recently, by whether they have dimethyl or diethyl group substitutions. *Methods:* We assessed variation in clinical presentation and outcome between different OP pesticides. All OP pesticide-poisoned patients admitted to secondary hospitals in north central Sri Lanka were observed prospectively for 18 months. Outcome and need for intubation were recorded for each patient. *Results:* 546 OP-poisoned patients were admitted; 71 died (CF 13%; 95%). The three most commonly ingested OPs were chlorpyrifos (CHL; n=234; diethyl OP, animal LD50: 135 mg/kg), dimethoate (DIM; n=122; dimethyl OP, animal LD50: 150 mg/kg) and fenthion (FEN; n=60; dimethyl OP, animal LD50: 586 mg/kg), all classified as having WHO Class II toxicity. Compared to patients poisoned with chlorpyrifos, patients poisoned with dimethoate and fenthion had greater need for intubation (CHL 12.4%; DIM 32.0%, Odds ratio 3.32 [95% confidence interval 1.9–5.7]; FEN 26.7%, OR 2.57 [1.3–5.1]) and higher case fatality (CHL 6.8%; DIM

21.3%, OR 3.69 [1.9–7.2]; FEN 16.7%, OR 2.73 [1.2–6.4]). Time to death and time to intubation differed markedly between different pesticides. In addition, speed of activation and speed of AChE inhibition appeared to be slower with dimethoate compared to chlorpyrifos OP, and S-alkyl OP inhibited AChE appeared completely unresponsive to oxime therapy. *Conclusions:* OP pesticides have generally been considered as a homogeneous group, varying only according to their animal toxicity. This study shows that OP pesticides vary significantly, and that this variation is important for ventilation and outcome. Each OP pesticide should therefore be considered separately, as an individual toxin, with major consequences for both pesticide regulation and clinical trials of new interventions for OP poisoning.

79. Treatment of Severe Organophosphate Poisoning in the Intensive Care Unit—Why Do the Patients Die?

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Objective: Analysis of the causes of death and the possibilities for their prevention in OP poisonings treated in ICU. *Methods:* Retrospective analysis of patients treated in ICU during 2-year period. The including criteria for admission was severe clinical picture (Poisoning Severity Score 3). Treatment included decontamination (gastric lavage, activated charcoal), antidotes (atropine and, if available, pralidoxime), sedation, and mechanical ventilation (MV) if needed. *Results:* Of 39 patients, 33 ingested dimethylphosphoryl compounds and 6 ingested diethylphosphoryl OP. MV was necessary in 24 cases (61.54%). MV started within 48 hours post-ingestion in 20 patients and lasted 1–12 days; there was single case of muscular weakness relapse and reconnection to MV. Four patients developed respiratory weakness after 3–5 days, and were ventilated for 2–40 days. Mortality rate among MV patients was 58.33% (14/24). There were no fatalities among the patients that didn't need MV, so mortality rate for the whole group was 35.59%. Ten patients died during MV treatment. MV allowed them satisfactory oxygenation, but cardiac arrest or irreversible cardiocirculatory shock lead to death in 8 patients within 1–3 days post-ingestion. A single patient, previously not treated by MV, developed respiratory arrest on day 5 post-ingestion, so after resuscitation was placed on MV. Unfortunately, her cortical brain was damaged and she died 40 days later. Two patients died within 7 days, one because of myocardial infarction, the other because of massive aspiration pneumonia. Three patients, previously disconnected from MV for several days, died during the third week of treatment; two developed massive pulmonary embolism, the third developed severe complications-pneumonia, sepsis, hemorrhagic ulcer and pseudomembranous colitis. The incidence of pneumonia (aspiration or ventilator associated) in MV patients was high (58.33%), but there was not significant difference between survivors and non-survivors. The mean age of non-survivors (61.3) was significantly higher than that of survivors (33.9). *Conclusion:* Respiratory muscle weakness, CNS depression and excessive bronchial secretion and spasm lead to hypoxemia and respiratory arrest—the most common causes of death in the early stage of severe OP poisoning. MV in combination with atropine for reversal of excessive muscarinic effects, could be life saving. However, cardiovascular disturbances, such as dysrhythmias, hypotension and shock can be irreversible despite the treatment. The intermediate syndrome, with respiratory muscle weakness, is unpredictable and may be fatal, but could be successfully managed by providing careful monitoring and adequate duration of ICU treatment. Patients who have been inactive due to prolonged MV and sedation may suffer thrombosis. Pulmonary thromboembolism can cause sudden death during recovery, and anticoagulant prevention may be indicated. Pneumonia is common complication, so adequate antimicrobial measures are necessary for its prevention and treatment.

80. Gastric Lavage—A ''Dying'' Therapeutic Procedure? Quality Control in a Regional Poisons Centre and Benchmarking Within European Poisons Centres

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Objective: Ten years ago gastric lavage (GL) was a ''gold standard'' in the management of poisonings. The Position Statement on Gastric Lavage changed the world of clinical toxicology. The aim of this study was: 1. To analyse the historical change and the current role of GL in the work of a poisons centre (PC). 2. To see the influence of scientific meetings on the activity of a PC. 3. To develop a quality assurance system for therapeutic procedures recommended by a PC, exemplarily for GL. 4. To start with

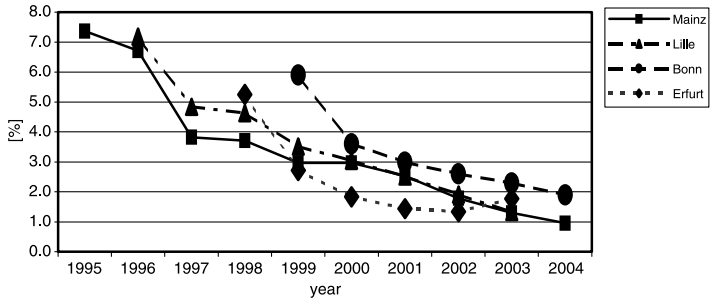

FIG. 1. Recommendation of gastric lavage in percent of all human poisonings per year in 4 poisons centres.

benchmarking in clinical toxicology. *Methods:* Documentation and evaluation of all cases of the Mainz PC with the poisoning documentation system ADAM©. Review of the indication for GL in all cases with recommended GL in the year 2003 by two experts and re-evaluation of every individual case by the consultant considering the indication criteria (''potentially life-threatening amount of a poison . . . within 60 minutes of ingestion''). Comparison of the assessments and discussion of the cases evaluated differently. Comparison of the regional data with data from other PC's. *Results:* From 1995-1-1 to 2004-11-20 the Mainz PC documented 196411 cases of human exposures. The frequency of recommendation a GL decreased from 7.4% in 1995 to 3.0% in 1999 and to 1.0% in 2004. The decrease was intensified after the publication of the Position Statement and after quality meetings of PC's focusing on GL. The self-assessment of 295 cases during the year 2003 with an advice to perform GL by 28 consultants of the Mainz PC revealed uncertainties about the indication criteria in about 20%. Most commonly in these cases the latency period between ingestion and call was greater then 60 minutes or the amount of the poison was not potentially life-threatening. The comparison of PC's is shown in Fig. 1. In all centres the frequency of recommendation for GL is decreasing The maximum range between the centres also decreased from 3.0 to 1.0%. *Conclusion:* The indication for GL assessed by a PC has continuously reduced over the last 10 years. A frequency of about 0.5 to 1.0 percent seems to be appropriate. This quality assurance system can be used for other therapeutic procedures in clinical toxicology. Its effectiveness has to be proved in future studies. The first step of benchmarking has been done. This procedure is a great challenge in clinical toxicology and helps us to understand and improve our work in every PC.

81. Respiratory Risks of Chlorination By-Products Contaminating the Air of Indoor Swimming Pools

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Chlorination is commonly used throughout the world to disinfect swimming pools. However, when chlorine compounds come into contact with organic material brought by swimmers, they generate a mixture of potentially harmful by-products which are inhaled by swimmers as gases or aerosols. When applying new non invasive tests to assess the effects of air pollution on the lung of children, we unexpectedly discovered that the regular pool attendance, especially by very young children, was associated with an increase of the lung epithelium permeability and of the risks of developing asthma. The main culprit appears to be trichloramine (NCl_3), an irritant gas building up in the air of poorly ventilated indoor chlorinated pools. Since these findings, we have undertaken a series of epidemiological and experimental studies in order to further assess the respiratory risks of chlorination products in indoor pools. The results of these studies confirm that regular attendance of indoor chlorinated pools is associated with a dose-dependent increase of the risks of developing allergic diseases such as asthma and eczema. These risks, however, appear to be largely restricted to atopic children who represent about 30–40% of the children population. Among these children, the asthma risk increases by about 60% for each 100 hours cumulated pool attendance. These estimates correspond to the attendance of an indoor pool with NCl_3 levels in the air in the range of 400–500 $\mu g/m^3$, which currently can be considered as an average level of air pollution for a public indoor swimming pool. These results were not biased by a greater propensity of atopic children or children with doctor-diagnosed asthma or from asthmatic parents to attend swimming pools. Interestingly, however, these risks appear to culminate when children and especially babies attend the small pool which is shallow, hot and usually more heavily polluted. The various experimental studies we performed on trained swimmers and animals confirmed that NCl_3 because of its water insolubility exerts its toxic action predominantly on the deep lung epithelium. By means of sensitive tests, we could estimate that this lung epithelium damage is likely to occur, even during strenuous swimming, only when the

NCl_3 concentration in the air exceeds a value of 300 μg/m^3. To prevent any respiratory risks, indoor chlorinated pools should be managed in order to maintain the levels of NCl_3 in air below this level, which can be easily achieved by adopting appropriate measures to avoid the formation of chloramines and to ensure their elimination from water and air. In addition, since the respiratory risks appear to stem largely from the attendance of the small pool by young children, the sanitation of these pools with a safer biocide than chlorine should be encouraged.

82. Improvements of the Documentation of Health Impairments Resulting from Chemical Industrial and Transportation Accidents

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Objectives: Any physician who has been appointed for the treatment or assessment of the consequences of an illness suspected of being ascribable to the effects of hazardous substances or hazardous preparations must inform the BfR about substances or preparations involved, cause of exposure, amount absorbed and symptoms/signs established (Chemicals Act § 16e). Thus the BfR can document data on exposure, symptoms/signs and clinical course in more than 2000 patients involved in more than 50 large-scale chemical (industrial) and transportation accidents in Germany. *Methods:* To improve the documentation of exposure, related health impairment and particularly, long-term consequences of chemical accidents, the data on a major transport accident with vinylchloride (VC) which took place in Germany in 1996 was re-analysed for better exposure documentation. *Results:* More than 325 persons were exposed to VC by this rail accident. For most of the patients, an exact exposure assessment was not possible, especially regarding long-term effects. As a consequence of these results, we feel that in the future, documentation of exposure data of chemical accidents has to be improved by additional instruments and methods. 1: Exposure levels should be measured in a practical time-dependent manner. Geographical measuring points should be fixed in the four cardinal points on two circles: The inner circle is to be placed around the area of the highest contamination (near the scene of the accident in the danger area, having a diameter of ca. 100—300 m) and depending on the geographical situation, a second outer circle of the accident in the outer perimeter of the accident (diameter of ca. 500–1000 m) should be drawn. 2: The exposure measurements should be performed at regular time intervals (e.g. 4 times within 24 hours) for as long as substances are released or a fire continues. 3: In addition, the most important exposure data should be collected by a special questionnaire which classifies the human exposure data by the same two categories as the data for the exposure measurements. Also measurements of blood and urine samples with indication date, time and method should be documented on the questionaire. 4: On the basis of a detailed map of the accident area (scale 1: 5000/1:10,000) and the duration of a person's stay in the danger area, the person-related exposure can be calculated and assessed in relation to the symptoms and signs seen. *Conclusion:* For chemical/industrial and transportation accidents, the DACP in the BfR has already improved the documentation standards. Corresponding documents will be published, e.g. a data form of time-related and place-related exposure measurements, a questionnaire and an accident scenario.

83. Pre-Hospital Management of the Poisoned Patient

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Objective: Patients with severe poisoning can develop significant clinical features soon after ingestion and so early, targeted management in the pre-hospital phase could be beneficial. This review will summarise the current literature on pre-hospital studies in toxicology. *Methods:* A PubMed and EMBASE search was undertaken using the terms pre-hospital, paramedic, toxicology, overdose and poisoning; relevant articles were retrieved and reviewed. *Results:* There have been relatively few studies that have investigated the role of pre-hospital management of the poisoned patient. Most of the literature is on pre-hospital naloxone for opioid poisoning and there has also been interest in pre-hospital activated charcoal (AC); this review will concentrate on these areas. *Pre-Hospital Naloxone:* Naloxone is widely used for in-hospital management of opioid poisoning. It has minimal toxicity and so it is particularly attractive as a pre-hospital antidote. The first large pre-hospital naloxone series described 813 unselected patients with a depressed level of consciousness who were given naloxone (0.4–0.8 mg). 60 (7.4%) had an improvement in level of consciousness and there were no significant complications associated with naloxone (1). Two more recent studies have assessed the use of naloxone in selected patients with clinical features to suggest

opioid poisoning. In the first, 726 patients who had 3 or more features were given naloxone. 94% responded and no complications of naloxone administration were recorded (2). The second study involved 730 patients with altered mental status and examined whether clinical criteria could predict response to naloxone. Overall 25 (3.4%) had a complete response and 32 (4.4%) had a partial response. Use of the clinical criteria had a sensitivity of 92% and specificity of 76% (3). Whilst IV naloxone is the treatment of choice for opioid poisoning in hospital, one of the concerns about IV naloxone pre-hospital is the risk of needle-stick injury (4,5). Several alternative routes of naloxone administration (e.g. intranasal, nebulised, endotracheal) have been investigated. A number of reports have described successful pre-hospital intranasal naloxone administration. In one series, 6 patients with heroin overdose treated with intranasal naloxone had return of spontaneous respiration within 2-minutes (6) In a further study, patients requiring pre-hospital treatment for suspected opioid poisoning were randomised to 2 mg intranasal (n=47) or 2 mg intramuscular (n=44) naloxone. Successful reversal of opioid toxicity was seen in both groups (7) There is a randomised controlled trial underway in Melbourne (reporting in 2005) comparing pre-hospital intravenous and intranasal naloxone in patients with opioid poisoning. *Pre-Hospital AC:* A number of recent studies have demonstrated delays in the presentation and assessment of poisoned patients and only 10% of patients in hospital receive AC within 1-hour (8–10). Pre-hospital AC administration has the potential to increase the proportion of patients who receive AC within 1-hour. However, in one series it was estimated that less than 5% of 2041 patients had potentially severe/life-threatening poisoning and were pickled up by an ambulance within 1-hour i.e. it is likely that pre-hospital AC is only going to be effective in a relatively small subset of patients. There have only been a few studies that have assessed pre-hospital AC administration. In a small retrospective review of 36 patients pre-hospital AC did not appear to have an impact on ambulance transit-time (11). One series described use of AC in the home in 115 children, 95% received AC within 1-hour; however this study included low-risk ingestions and so is not representative of the population in whom AC is indicated. The largest series describes 500 poisoned patients who received pre-hospital AC, this has only been published in abstract from and so limited data were presented. 10% were intubated and received AC via a naso-gastric tube and 10% refused to drink the AC (13). We are currently undertaking a study investigating the use of pre-hospital AC in London. *Conclusions:* Naloxone is a safe and effective antidote when used in selected patients with opioid poisoning in the pre-hospital environment. The intravenous route is currently the route of choice but intranasal naloxone has a number of potential advantages and a randomised controlled trial comparing these two routes is currently underway. There is currently insufficient data to recommend pre-hospital AC, but studies are currently underway assessing its role. Ambulances are never going to be able to hold all antidotes or offer wide ranging care for all poisoned patients and so future studies should assess the role of targeted pre-hospital management of selected patients with severe poisoning. *References:* 1. Yealy DM, Paris PM, Kaplam RM, et al. The safety of prehospital naloxone administration by paramedics. *Ann Emerg Med* 1990; 19:902–905. 2. Sporer KA, Firestone J, Isaacs SM. 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84. Pesticide Surveillance Using Poisons Telephone Service and TOXBASE, An Internet Database—First 6 Months of a Pilot Project

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Objectives: To investigate methods of improving reporting of pesticide related incidents using UK National Poisons Information Service (NPIS) resources. *Methods:* All pesticide enquiries to NPIS, Edinburgh telephone enquiry service

between 1 April and 30 September 2004 were followed up by postal questionnaire to obtain further details of the incident. For the same time period all accesses to 174 agrochemicals and pesticide products on TOXBASE (Internet poisons database) were electronically notified to NPIS, Edinburgh in real time, as part of a pilot project. Users accessing these pesticides for a patient related enquiry were requested to complete an on-line form (available from 7 May). If no on-line form was completed at the time of contact a postal questionnaire was sent to the registered TOXBASE user for that department/GP surgery but since patient/enquirer details were not available identification of the incident was not always possible. Postal questionnaires were not sent to NHS Direct/24 (public access telephone health enquiry services with nurse advisors using computer algorithms) because of lack of contact details and because of patient confidentiality (641 product enquiries). Many of the enquirers consulted >1 pesticide or the same entry several times and all pesticide accesses within a 30 minute period (approximately) for one user were included on one follow-up questionnaire. *Results:* Pesticides do not form a large part of the work of poisons centres in the UK. Between 1 April and 30 September 2004 NPIS, Edinburgh received 1820 telephone enquiries, mainly from Scotland, and pesticides represented 3.7% of product enquiries. Forty-five pesticide-related telephone enquiries were followed up and 24 returns (53.3%) received to 1 November. In the same period TOXBASE, the UK Internet poisons database received 436,334 product accesses of which 13,296 (3.0%) were to pesticides. 2610 electronic notifications of pesticides of interest were received and concerned 1891 different pesticide product accesses. 159 electronic forms were returned (9.4%). These came from public access telephone enquiry services (126; 79.2%); hospitals (24; 15.1%); poisons centres (8; 5.0%); general practitioner (1). The return rates for each group were: public access telephone enquiry services (126/574; 22.0%); hospitals (24/857; 2.8%); poisons centres (8/244; 3.3%); and GPs (1/16; 6.3%). 997 postal questionnaires were sent out and 326 (32.7%) replies received. Of these 286 (28.7%) concerned pesticides exposures (remainder education, duplicate patient or not pesticide-related). Return rates were: hospitals (184/781; 23.6%); poisons centres (86/177; 48.6%); GPs (5/17; 29.4%); and veterinary services (11/20; 55.0%). *Conclusions:* Nurse advisors from public access telephone enquiry services, who use computers to help answer their enquiries, are more likely to return on-line forms than other users. A better return rate was found after telephone enquiries as contact details were available. A combination of on-line forms and follow-up questionnaires can increase surveillance of pesticide-related incidents, which would otherwise not be collected.

85. QRS-Dispersion in Patients with Acute Digoxin-Intoxication

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Background: The depolarization and repolarization of the ventricular muscle system is changed pathologically in acute digitalis intoxication due to the excessive calcium overload. Similarly, in chronic cardiac insufficiency the intracellular calcium concentration of myocardial cells increases. Determination of QRS-dispersion is used for estimation of risk of sudden death in case of chronic heart failure and left ventricular hypertrophy. Measuring QRS-dispersion is simpler and the inaccuracy is less than using corrected QT-dispersion. *Objective:* to determine the value of QRS-dispersion in patients with acute digitalis intoxication for prognostic assessment, retrospectively. *Patients and Methods:* The interlead variability of the QRS-complex and QT- and JT-interval were measured manually from standard 12-lead ECGs, recorded at 25 mm/s, analysed by one observer, blinded to the clinical history in 19 patients with severe acute digoxin intoxication (group 1, Poison Severity Score 3 or death, average age 51.61 ys, 6 males, 13 females, serum digoxin level 2.0–35.2 ng/ml, average serum level 15.54 ng/ml), in 28 patient with mild to moderate acute digoxin intoxication (group 2, Poison Severity Score 1–2, average age 50.43 ys, 10 males, 18 females, serum digoxin level 2.11–8.98 ng/ml, average serum level 4.88 ng/ml), in 30 patients with hyperkalaemia (group 3, no digoxin therapy or toxicity, average age 49.41 ys, 12 males, 18 females, serum potassium level 5.60–7.5 mmol/l, average serum level 6.21 mmol/l), in 30 patients with chronic digoxin therapy without signs of toxicity (group 4, average age 58.13 ys, 11 males, 19 females, serum digoxin level 0.5–1.81 ng/ml, average serum level 1.03 ng/ml) and in 30 control subjects with no underlying heart disease (group 5, average age 41.36 ys, 10 males, 20 females). ECG records performed at the admission to the hospital. The patients with fascicular block, left ventricular hypertrophy and severe left ventricular dysfunction were excluded out of the patients treated with digoxin ingestion at our department in the last 10 years. *Results:* see Table 1. *Conclusions:* In acute digoxin intoxication the extent of QRS and QTc-dispersion measured on 12-lead ECG is a potential marker of intracellular calcium overload and it correlates well with the severity of poisoning. Measurement of QRS-dispersion is simpler and less inaccurate than that of QTc. Determination of QTc-dispersion can be useful if fascicular block, left ventricular hypertrophy and systolic dysfunction exist.

TABLE 1
QRSD: QRS-dispersion, QTcD: corrected QT-dispersion, JTD: JT-dispersion

	Group 1	Group 2	Group 3	Group 4	Group 5
QRSD	36.84±11.56	23.93±8.03	19.13±11.42	19.01±9.16	18.55±6.12
QTcD	87.07±33.73	53.31±18.53	47.38±16.12	47.42±14.81	38.41±9.60
JTD	88.75±38.46	64.64±30.48	46.44±15.28	59.13±26.21	30.91±11.44
QRSD>30 ms	13/19	3/28	2/30	1/30	1/30
>40 ms	4/19	0/28	1/30	0/30	0/30
QTcD>65 ms	16/19	7/28	5/30	3/30	0/30
>100 ms	6/19	1/28	3/30	1/30	0/30

86. Adrenaline Is Not the Drug of Choice for Severe Cardiovascular Failure in Beta-Blocker Poisonings

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Objective: Cardiovascular assist device has been used in poison-induced cardiovascular shock refractory to maximal catecholamine therapy. High doses of adrenaline are usually used to define the maximal catecholamine therapy assuming, therefore, that adrenaline is the drug of choice in severe shock. We report 4 cases of beta blockers-induced shock in which adrenaline had to be weaned and replaced by other catecholamines. *Case Reports:* Case 1. Poisoning by an unknown amount of propranolol in a 76-year-old woman. When the emergency medical unit arrived at home, 5 to 8 hours post ingestion, the patient was comatous (GCS 3) with a blood pressure (BP) not recordable. Treatment included mechanical ventilation, adrenaline 1 mg iv followed by an infusion of 0.4 μg/kg/min. Examination on admission: coma (GCS 3), BP=105/80 mm Hg, heart rate (HR)=43/min, cyanosis and vasoconstriction of the extremities. Swan Ganz catheterism performed 2 h post admission showed a severe cardiogenic shock: BP=117/82 mm Hg, HR=33/min, cardiac index=0.72 L/min/m^2, POAP=18 mm Hg, SVR=8878 dynes/cm^{-5}/sec. Adrenaline was withdrawn over 8 hours and replaced by isoproterenol (4–30 mg/h) and dobutamine (5–24 μg/kg/min). Hemodynamic condition improved progressively, catecholamines were withdrawn on the 3rd day, and the patient recovered. Case 2. A 77-year-old man ingested 5.6 g atenolol. On arrival of the emergency medical unit, he was comatous with a HR=30/min and a BP=70/35 mm Hg. He was treated by mechanical ventilation, vascular filling and adrenaline 0.5 μg/kg/min. A Swan Ganz catheterism 2 h post admission showed a severe cardiogenic shock: cardiac index=2.99 L/min/m^2, POAP=20 mm Hg, SVR=2752 dynes/cm^{-5}/sec. Adrenaline was withdrawn over 7 hours and replaced by dobutamine (20 μg/kg/min). Cardiovascular failure improved and dobutamine was stopped on day 3. The patient recovered completely. Case 3. A 81-year-old woman ingested 4 g acebutolol. Two hours post-ingestion she was comatous (CGS 3), BP=65/25 mm Hg, HR 60/min. Immediate treatment included mechanical ventilation, vascular filling and adrenaline (0.3 μg/kg/min). On admission: coma (CGS 3), mechanical ventilation, vasoconstriction of the extremities, BP=100/65 mm Hg, HR=64/min. A Swan Ganz catheterism 2 h post admission showed: cardiac index=2.89 L/min/m^2, POAP=14 mm Hg, SVR=1689 dynes/cm^{-5}/sec. Adrenaline was rapidly withdrawn over 1 hours and replaced by isoprenaline (2 mg/h) and norepinephrine (0.2 μg/kg/min). Catecholamines could be stopped on the 3rd day and the patient recovered uneventfully. Case 4. A 38-year-old woman ingested 5.23 g betaxolol, 30 mg lorazepam and alcohol. On arrival of the emergency medical unit, she was comatous (GCS 3), cyanotic with a BP of 90/70 mm Hg and a HR of 65/min. Immediate treatment included mechanical ventilation, vascular filling and adrenaline 1 mg iv followed by an infusion (0.4 μg/kg/min). On admission: coma (GCS 3), HR=65/min, BP not recordable which needed immediately adrenaline, isoproterenol and norepinephrine iv infusions. Swan Ganz catheterism 2 h post-admission showed a severe cardiogenic shock: cardiac index=0.9 L/min/m^2, POAP=30 mm Hg, SVR=4300 dynes/cm^{-5}/sec. Despite aggressive treatment with adrenaline (4 μg/kg/min), isoproterenol (0.08 μg/kg/min), noradrenaline (1.8 μg/kg/min) shock persisted and a cardiac echography showed a complete akinesis of the left ventricle. Cardiovascular support by percutaneous cardiopulmonary bypass (ECMO) was initiated and maintained during 78 hours. Shock progressively improved and vasoactive drugs were withdrawn on day 5. The patient recovered slowly over one month. *Conclusion:* Adrenaline is often used for the treatment of shock in antiarrhythmics poisonings. In our cases, adrenaline used as first line treatment did not improve the shock. Hemodynamic parameters revealed in all cases a severe cardiogenic shock with especially high systemic vascular resistances. Adrenaline has beta and alpha mimetic effects which can not be titrated separately. In 3 cases the withdrawal of adrenaline and replacement by betamimetic drugs (isoproterenol or dobutamine) associated with norepinephrine

resulted in an improvement of the cardiogenic shock. Our cases suggest that adrenaline, despite its inotropic effect may worsen cardiogenic shock by increasing strongly the systemic vascular resistances (after-load) and may have a deleterious effect in severe beta blockers poisonings.

87. Copper Sulfate Intoxications in Toddlers and Teenagers

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Objective: Acute copper sulfate intoxications have been described frequently. Many poisonings are reported from India, where copper sulfate is frequently used in suicide attempts. In the Netherlands, as in most western countries, copper sulfate poisonings are rare, although copper sulfate itself, having many agricultural, industrial and pharmaceutical applications, is readily available. However, recently the Dutch Poisons Information Centre received several requests for information regarding pediatric and teenager exposures to copper sulfate. Copper sulfate is corrosive to skin and mucous membranes. After ingestion symptoms generally occur within 15 minutes to 1 hour. Initial symptoms include abdominal pain, nausea, vomiting, diarrhea, salivation, and metallic taste, in severe cases with corrosive injury of the gastrointestinal tract leading to bleeding, perforation, hypotension, and hemolysis. Refractory shock and hepatic and renal failure with coma may develop after several days. *Case Series:* In 2003–2004 19 cases were reported to the Dutch Poisons Centre. Six children under 4 years of age, nine teenagers and four adults were involved. The routes of exposure were ingestion (12 cases) or eye-contact (7 cases), but especially the circumstances of the exposures attracted our attention. Several young children ingested a copper sulfate containing product used as a disinfectant in farms. They either ingested granules or a solution of copper sulfate (somethimes with formaline). In a few other cases children ingested a copper sulfate solution used for algae-control in aquaria. In teenagers most intoxications occured while performing chemical experiments at school. Several girls took a sip of a copper sulfate solution, others had splashes in the eyes. Copper sulfate may also be found in children's chemistry sets and mineral gardens. In most cases only minimal symptoms occured. However serious intoxications are possible, as is illustrated by the following case reported in March 2004. In this heavy exposure case the advice of the Poisons Centre to immediately measure serum copper levels and, if indicated, start chelation therapy was neglected. A 2-year old boy ingested an unknown amount of copper sulfate (used as a disinfectant) which he found on the stable-floor. He immediately started to vomit. Upon arrival in the hospital a soporeus, pale boy was seen with a decreased saturation. Laboratory investigations revealed renal and hepatic injury and on day 3 of hospitalization he became anuric and was transferred to the Intensive Care department of another hospital for hemodialysis. Over the next week the condition of the patient improved gradually and he made a full recovery. *Conclusions:* In the Netherlands most intoxications with copper sulfate are accidental intoxications in young children in farm surroundings or in teenagers at chemistry experiments at school. It seems that copper sulfate is mistakenly considered by some people, including docters, to be a fairly harmless compound. Especially farmers and chemistry teachers should be more alert for possible risks of these compounds. In severe poisonings chelation therapy should be considered.

88. Acute Chromic Acid Poisoning Treated with Haemodiafiltration

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Objective: Acute oral poisonings with hexavalent chromic acid are infrequent and have a high fatality rate. Extracorporeal elimination procedures show rather inconsistent results. This report describes the clinical course and the analytical data of a severe acute chromic acid poisoning treated by haemodiafiltration (HDF). *Case Report:* In a suicide attempt a 23-year-old galvaniser drank 100–150 ml chromic acid 3.67% together with 2 bottles of wine. The patient initially developed recurrent vomiting, abdominal pain, and profuse bloody diarrhoea, followed by respiratory insufficiency, bleeding disorder, renal and hepatic failure. On day 3 hepatic function deteriorated to such an extend that the patient was listed for high urgency liver transplantation. However, under the treatment with intermittent HDF, N-acetylcysteine, fresh frozen plasma, red-cell and

platelet transfusions liver transplantation could be avoided and from day 4 the patient recovered increasingly. Intermittent haemodiafiltration was performed 6 hours daily with a dialysis fluid flow of 800 mL/min and a predilution of 60 L each. On admission the patient had a chromium level in whole blood of 7260 μg/L, in serum of 3000 μg/L, in red blood cells of 12907 μg/L, in urine of 8920 μg/L and in stool of 7830 μg/L. Before the 1st HDF the chromium half-life in serum was 81.6 hrs, the renal clearance ranged between 1.2 mL/min and 4.2 mL/min and the faecal clearance was 3.9 mL/min. During the following HDF treatments the chromium concentration in serum decreased considerably with an half-life of 6.5 hrs. For the first 3 HDF treatments the average clearance over 6 hours was 53 mL/min with the highest values of more than 60 mL/min at the beginning of each HDF. Between the haemodiafiltrations chromium concentration in serum re-increased significantly. *Conclusion:* We still do not know the toxicological relevance and clinical benefit of lowering chromium concentration in serum, but as long as renal-replacement therapy is required anyway, it seems reasonable to choose that procedure which decreases chromium concentration most effectively. Unfortunately the reports about haemodialysis in chromium poisoning are controversial and show altogether rather poor results. This is the first case report about the application of HDF in chromium poisoning showing that this treatment seems to be superior to other elimination procedures.

89. Severe Acute Poisoning with Cypermethrin and Xylene

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Objective: Severe poisoning with pyrethroids is observed rarely. Although He et al. (1989) reviewed 573 poisonings caused by pyrethroids from Chinese literature, little is known on symptoms of distinct substances. We report on a severe intoxication caused by the type II pyrethroid cypermethrin, identified by toxicological analysis. *Case Report:* A 72 year old male patient presented at the hospital with confusion, nausea, abdominal cramps, vomiting, salivation, and tremor after accidental oral uptake of an insecticide at a farm. Bromophos was suspected first, but no decrease in plasma cholinesterase activity could be detected. 2 h after ingestion the patient developed generalized seizures and subsequently convulsive status epilepticus. He was treated with propofol and thiopental. A systematic toxicological analysis was performed and cypermethrin and xylene (besides propofol, thiopental, and pentobarbital) could be detected in aspirate from stomach and in urine using gas chromatography coupled with mass selective detection system (GC/MS). A commercial agricultural product containing cypermethrin and xylene available in German market could be identified. 15 h after ingestion the patient awoke; at day 2 no remaining neurological deficiencies could be detected. The patient was further treated with 3×400 mg valproic acid daily and was discharged on day 4. *Discussion:* Oral intake of pesticide products may lead to severe poisoning of short duration with prominent symptoms of the central nervous system when caused by pyrethroids, typically formulated with an organic solvent. A convulsive status epilepticus caused by a pyrethroid is a rare event and has not been reported earlier. A toxicological screening analysis using GC/MS technology can rapidly identify even rare poisons not suspected initially and thus help to avoid expensive diagnostic procedures. *Conclusion:* Initial symptoms of oral cypermethrin poisoning, especially salivation and seizures, may be misinterpreted as symptoms of organophosphate poisoning. In these cases laboratory investigations can rapidly lead to correct diagnoses. *Reference:* He F, et al. Clinical manifestations and diagnosis of acute pyrethroid poisoning. *Arch Toxicol* 1989; 63:54–58.

90. Survival of 2,4-Dinitrophenol Induced Hyperthermia

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Objective: 2,4-dinitrophenol (DNP), a potent uncoupler of oxidative phosphorylation, has notoriously caused severe morbidity and mortality when used as a dietary aid. Although banned by the FDA, it is still available for purchase over the Internet. We present a rare case of survival following severe DNP toxicity. *Case Report:* A 28-year-old male presented with dyspnea, fever, flushing, diaphoresis and excessive thirst for 2 days. He had consumed 27 DNP capsules (obtained over the Internet) over 6 days as part of a body-sculpting, weight-loss regimen. Abnormal physical findings were: blood pressure, 156/66 mm Hg; heart rate, 109 beats per minute; respirations, 24 breaths/minute; temperature, 102.2°F; and yellow-tinged diaphoresis. There was

laboratory evidence of rhabdomyolysis and AST elevation. Treatment included intravenous fluids, benzodiazepine sedation, active cooling measures, and urinary alkalinization. Despite this, hyperthermia and muscle cramping progressed ($T_{max}=105°$), and shivering was uncontrollable with high-dose benzodiazepines. Neuromuscular blockade was ultimately required. Hyperthermia recurred each time attempts were made to decrease active cooling measures over the next 11 days. Other complications included deep venous thrombosis, retroperitoneal bleeding, and sepsis. The patient remained neurologically normal and was extubated on day 9. He finally defervesced on day 11, and was discharged to home on day 24. *Conclusion:* Although a banned chemical, DNP continues to be used as a dieting aid and is widely available via the Internet. Survival following severe toxicity is unusual, but possible with aggressive cooling measures and maximal supportive care.

91. Eye Exposure to Chemical Products

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Objective: Five percent of the inquiries to SPIC are related to eye exposures, most commonly caused by chemical products. The aim of this descriptive study was to gather and evaluate information about the circumstances of the accidents, the chemical ingredients involved, the severity of eye injury and the compliance to advice given. *Methods:* All telephone calls concerning eye exposure to chemical products were registered during the three months period, January 15 until April 15, 2004. Follow up interviews were performed where the telephone number was registered at the first contact. Case records with connection to inquiries from medical professionals during the period were also studied. Severity of symptoms were graded according to the Poisoning Severity Score (PSS) in none, mild, moderate and severe poisoning. *Results:* Inquiries related to 587 cases were recorded. A follow up was possible to perform in 247 cases (214 by interview and 33 by case records). Interviews could not be carried out in the remaining cases due to failure in obtaining telephone numbers or refusal to participate. Sixty percent of the calls came from the general public, 33% from different health care facilities and 7% from work places and others. There was a predominance for adults. The main groups of chemicals involved were: hydrocarbons (13%), surfactants (12%), alkali (11%), alcohols (10%), acids (6%) and miscellaneous corrosive chemicals (5%). Cleaning products, gasoline and hygiene products were the most common product types. The eye injury in cases evaluated through telephone interview (n=214) was graded as none in 13, mild in 183 and moderate in 18 patients. No exposure resulted in severe damage in the interviewed group. Of patients reported to the centre by case records no injury was observed in 4, mild in 18, moderate in 9 and severe injury in 2 patients. Injuries graded as moderate were most commonly caused by cleaning products containing sodium hydroxide. The two cases graded as severe were caused by cement products containing calcium oxide/calcium hydroxide. The case records from health care facilities were related to non-occupational exposure in 9 cases and to exposure at work places in 24 cases. Advice given to the general public by SPIC, i.e. instructions about rinsing or advice to seek medical attention was followed by 79% of the callers. *Conclusions:* Although the number of inquiries to SPIC concerning eye exposure to chemicals is quite high, accidents in the home setting are not a serious medical problem. In the majority of cases there were only no or mild symptoms. Immediate rinsing with water at home on advice from the poison centre is usually sufficient. In spite of the knowledge of risks and the availability of protective measures, occupational eye injuries frequently occur and these patients show more severe symptoms.

92. Steroid Use in Oral Caustic Exposures

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Objective: The role of corticosteroids in the management of corrosive chemical ingestions is controversial. This survey was undertaken to determine the practices of regional poison centers (RPCs) regarding the use of steroids for such ingestions. *Methods:* A standardized survey tool was developed. The survey was sent to the medical directors of 59 RPCs in the United States. A reminder notice to complete the survey was sent out 2 and 4 weeks after the initial e-mail. *Results:* A total of 33 poison centers completed the survey (56% response rate). 63% (21/33) do not recommend steroids for any caustic injury. Eighteen percent (6/33) of the respondents routinely consider the use of steroids after oral caustic exposures. One center recommended their use prior to obtaining endoscopy, while the other 5 centers would only recommend steroid use after endoscopy. The remaining centers did not follow a consistent policy. Based on endoscopy results, 100% (6/6) recommended steroid use in 2nd

degree burns, and 50%, (3/6) recommended their use for circumferential burns. No respondents used steroids for 1st or 3rd degree burns. For steroids to be recommended by the RPCs, 30% (10/33) of respondents need physician approval (medical toxicologist or toxicology fellow), while 6% (2/33) of respondents allow specialists of poison information to make the recommendation. Only 6% (2/33) of the respondents had a formal written protocol for dealing with oral caustic exposures. *Conclusions:* Routine steroid use for the management of oral caustic burns remains controversial in toxicology. Only 18% of RPCs actually recommend their routine use, and only a small fraction have written treatment protocols. Still, the practices are varied in this sample of United States RPCs. The centers who do recommend the use of steroids are very specific about the indications and approval process.

93. Toxic Dermatitis After Accidental Dermal Contact with Elemental Mercury

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Objective: To present a case with dermal effects following direct skin contact with elemental mercury. Metal mercury has been shown to be a dermal sensitizer after inhalatory, digestive, and parenteral exposure, besides skin direct contact. Immunologic mechanisms for this fact have not been well understood yet. *Case Report:* We present a case of direct metal mercury contact in a 18 year old man, who kept around 5 ml of metal mercury in a glass container into his pocket for 36 hours, without noticing it leaked during this period. The leakage made the mercury to soak his trousers allowing the mercury to be in contact with an extensive part of his left leg and foot skin, for a sufficient time to produce an erythematous, edematous, and vesicular dermatitis. These lesions evolved to erythematous plaques with small scattered areas suggesting necrosis or drying vesicles lesions, after a week (photos of the observed skin lesions will be shown to illustrate the case). Some distant lesions were also seen in the right forearm and chest. Distant papulo-erythematous and vesicular lesions were seen in the thorax and abdomen. Patient complained of mild local pruritus and burning sensation in the affected areas. No other symptoms were referred. Urinary mercury was measured in two spot urine samples, using AAS-HG, one in the first day of clinical evaluation (Day-1), and the second, a week later (Day-7). Urinary Hg results showed: Day-1 = 5.9 μg/L, and Day-7 = 19.6 μg/L. These results might indicated that some sort of dermal absorption occurred, as the inflammatory process of the skin could have compromised the natural protection barriers against absorption of non fat soluble substances, like elemental mercury. Systemic corticosteroids were prescribed, but patient did not show up for follow-up. *Conclusion:* Toxic dermal effects due to elemental mercury must be expected after direct contact of the skin. Washing using profuse water should be advised in order to prevent dermatitis and further mercury absorption.

94. DMSA Chelation Therapy in a Patient with Accidental Elemental Mercury Arterial Embolism

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Objective: To describe a case of arterial mercury embolization with mild symptoms, but high Hg urinary levels for three years treated with DMSA for 12 days with a rather good Hg excretion. *Case Report:* In November 2001, a 56 old man, suffered mercury arterial embolization into his left radial artery during measurement procedure for mean arterial pressure, in a graft coronary bypass surgery. He felt excruciating pain in his left hand and arm when 3 to 6 ml of elemental mercury was driven to his radial artery by accident. After 20 days he had three distal phalanges, from the 3rd, 4th and 5th left hand fingers, amputated due to ischemic tissue necrosis. He reported that a rather significant amount of mercury has leaked from his fingers before amputation. He presented himself to our hospital 3 years after the accident complaining of chronic headache, memory loss, irritability, and general mialgia. Neurological examination showed no tremor of extremities, good static and dynamic balance, normal walking, and no motor or sensitive deficits. Neuropsychological evaluation showed mild alterations of recent memory, constructive praxis and mental rotation of figures, suggesting a likely dysfunction of left cerebral parietal inferior region, not

necessarily due to Hg intoxication, and most probably related to an old ischemic episode. Renal function assessment showed beta-2-microglobulin level of 0,23 mg/dL (RV between 0,07 and 0,18). All other laboratory parameters were normal. Radiographic evaluation showed mercury deposits in the left hand and forearm, and sparse opaque micronodules in the lungs. Urinary Hg levels: Jan. 2001=200 μg/gC; Nov. 2003=138.5 μg/gC; Jan. 2004=254,0 μg/gC. DMSA 600 mg/day in three doses was prescribed in March 2004. Hg urinary levels prior to treatment were: Jan. 2004=252 μg/L, and Mar. 2004=167,0 μg/L (mean=169.2 μg/L). Mean urinary Hg during 12 days of treatment was 541.7 μg/L (982,0 μg/24 hs). No side effects were observed during the whole period of treatment. *Conclusion:* Although DMSA is not the best chelating agent for mercury according to the literature, its use in this case showed an increase in mercury excretion of 3.2 times, without side effects.

95. An Occult Migrating City Gas Leak Causing Significant Carbon Monoxide Poisoning in Firefighters

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Case Series: 15 experienced firefighters from a local fire-station in Copenhagen were brought into the emergency department at 04.00 hours with symptoms of CO poisoning of varying severity. One firefighter had woken up with severe headache, confusion and nausea and managed to call for help before involuntarily urinating and passing out. The fire-station was not on fire and had no gas supply. Despite several missions during the day, the only place common to all poisoned firefighters was their own station. A gas leak had been noted earlier that day but was located 280 m from the station and had been contained by the gas company. On arrival back to the station late at night, one firefighter had noted a faint smell of gas but attributed it to an odour in his clothes from a minor exposure earlier in the day, where the gas smell had been heavy. Initially, due to the location of a governmental office in the proximity, a terror action in the neighbourhood could not be ruled out. A large-scale investigation involving the gas company, police and fire departments was initiated to try to locate the source and evaluate the need for evacuation of the area. >270 flats were investigated. Gas from the earlier leak (high pressure pipes, 2% CO) had formed an underground pocket and due to an up-wards slope of 3%, migrated to the fire-station and entered the building through telecommunication cable-channels. On investigation, gas was found up to 500 m away from the location of the leak. 7/15 firefighters were treated with hyperbaric oxygen and one fire fighter (CO-Hgb 36% on arrival) still suffers sequelae (memory deficits and neurological problems in an upper extremity). *Conclusion:* The combination of 15 firefighters seeking medical attention in the middle of the night with symptoms of CO poisoning with no known exposure and no civilian casualties, initiated a large-scale investigation that revealed an underground migration of gas over a long distance through wet soil, which eliminated the olfactory warning. The incident has led to the sealing of cable-openings with foam and to the installation of CO detectors in fire-stations.

96. Caustic Lime Used as Desiccant in Chinese Cookies Box Mistaken for Sugar Powder

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Introduction: Desiccants are widely used in different kind of products (electronic devices, shoes, bags, suits and more recently food) for preventing damage by humidity. Poison centers all over the world receive every year a huge number of phone calls after ingestion of that substance in particular in children. Silica gel (a siliconic polymer) is the substance almost always used and appreciated by toxicologists for the total absence of toxicological risk. But in the last few years, with the diffusion of products from China, is emerging the risk of caustic lime desiccant use. A previous abstract (1) presented a case-report about the ingestion of caustic lime desiccant found in a Chinese cookies box by a child. We present a second case-report underlying the high risk of caustic lime used as desiccant in food products. *Case Report:* Our Poison Center received a call from a local hospital about two young female patients who have eaten erroneously the caustic lime desiccant packet found in a box of Chinese cookies. The $Ca(OH)_2$ was put by the women on the cookies as sugar and then they ingested only one cookie each. The two patients showed mild symptoms: nausea, irritation and erythematous oropharynx, but the gastroscopy performed in the following day was negative for both the patients and they were discarged after symptomatic treatment (proton pump inhibitor infusion and aluminium and magnesium hydroxide oral administration). *Conclusion:* Although on the packet words state 'DO NOT EAT' and 'CAUSTIC LIME DESICCANT', the risk of the use of caustic lime as desiccant in food boxes can determine an

ingestion after mistaking for sugar. International regulatory agencies for food safety should prohibite the use of caustic lime desiccant in food boxes, substituting that with the totally safe silica gel. We want also underline the use of small packets of oxygen indicators (colourimetric) in Chinese cookies boxes and we are waiting for the first patient after their ingestion. *Reference:* 1. Schier JG, Hoffman RS, Nelson LS. Desiccant induced gastrointestinal burns (abstract). *J Toxicol Clin Toxicol* 2002; 40:627.

97. Professional Hand Cleansers—Experience of the National Poisons Information Service (London)

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Objective: In order to reduce infection rates in National Health Service (NHS) hospitals in the UK, by April 2005 alcohol-based hand sanitisers will be placed at the entrances to wards, at bedsides and be carried by staff throughout the NHS. In anticipation of wider use and availability of such products, surveillance of enquiries to the London Centre of the National Poisons Information Service (NPIS[L]) regarding these products has been instigated. In preparation, past experience regarding such products was reviewed. *Methods:* A retrospective review of enquiries to NPIS[L] regarding professional hand sanitisers in the past five years (1999 to 2003) was undertaken, by searching the NPIS[L] database for enquiries relating to professional hand cleansers. *Results:* The NPIS[L] received 108 enquiries concerning professional hand cleaners from 1999 to 2003, 0.02% of all enquiries for that period, and at least 70 were alcohol-based products. Enquiries regarding these products have remained relatively constant (average 21 calls per year, range 16–25) despite a decrease in overall enquiry numbers, representing a proportional increase of 4 fold from 1999 (0.01%) to 2003 (0.04%). All enquiries received involved adults, usually following ingestion (59, 55%) or eye exposures (33, 31%). Ingestions were intentional in 25 (42%) cases (11 (19%) self harm attempts and 7 (12%) abuse attempts due to the alcohol content, 7 (12%) unknown); accidental in 27 (46%) cases and not stated in 7 (12%) cases. 16 (27%) ingestions occurred at home, 1 (2%) at work and 30 (51%) occurred in care homes; in 12 (20%) the location was not stated. Following ingestion symptom severity was low (22 (37%) asymptomatic, 16 (27%) mild symptoms, 20 (34%) not stated). However there was 1 serious case in 1999. The patient ingested an isopropanol-based product and suffered hypotension, drowsiness, hypoventilation, tachycardia and confusion; the outcome of this case is unknown. All 33 eye exposures were accidental; 20 (61%) were occupational accidents. Following eye exposures minor eye irritation (21, 64%) was most commonly reported. *Conclusion:* Poisoning due to alcohol-based hand sanitisers is uncommon and rarely serious. However, there is potential for self-harm or abuse with these products and serious clinical effects can occur. The introduction of these products widely in hospitals means that they will be more available to patients who may misuse them. Their increased use may also result in more adverse effects occurring occupationally in hospitals.

98. Thallium Poisoning: from Diagnosis to Long Term Effects

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Objective: To describe clinical course and long term outcome of a series of thallium poisoned patients. *Case Series:* A 50-year-old man came to the emergency department (ED) complaining of severe abdominal pain, chest tightness, loin-sacral pain, paresthesiae in lower extremities and worsening hyperesthetic pain in stocking-and-glove distribution. Bioumoral and instrumental tests for inflammatory or autoimmune neurologic diseases were normal. Toxic etiology was suspected because of the presence of similar though lesser symptoms in other five persons who shared the same meal three days before. Investigations revealed consumption of red wine given as a present but contaminated with Tl for criminal purpose. The severity of symptoms (Table 1) was related with the amount of wine ingested excepting a young bulimic patient (pt. n. 6) who could decontaminate herself by early vomiting. Neurotoxicity developed in the most severe case (pt. n. 1) as a distal, sensory-motor neuropathy accompanied by psychiatric disturbances including insomnia, anxiety, allucinatory and paranoid symptoms. Sensory and motor alterations were accentuated in the legs with intense pain, paresthesias progressive weakness, difficulty in walking and paralysis. Less severe cases showed distal sensory loss, muscle pain, signs of diminished muscle strength, and fatigability. All six patients were treated with the antidote Prussian blue (250 mg/kg/die) until urine thallium levels had returned to background values, reached after 83, 48, 23, 20, 10 and 9 days respectively. At 3 years after poisoning, clinical and instrumental follow-up

Table 1

Patient	1	2	3	4	5	6
Wine consumed (ml, estimated)	300	170	80	80	20	70
Chest tightness	+	+	+	+	+	+
Early onset paresthesias	+	+	+	+	+	+
Constipation	+	+	+	+	−	−
Hair loss	+	+	+	+	−	−
Polyneuropathy	+	+	−	−	−	−
Paralysis and respiratory failure	+	−	−	−	−	−
Psychiatric symptoms	+	−	−	−	−	−

documented incomplete restitutio ad integrum in two patients. *Conclusion:* Thallium poisoning is a rare but potentially fatal event. Despite restrictions on the use of thallium in rodenticides, cases still occur from homicidal attempts. The clinical syndrome of thallium poisoning is well defined, but the diagnosis is often difficult until alopecia develops. Thallium poisoning should be suspected in patients with unexplained gastrointestinal symptoms followed closely by distal paresthesiae, especially if they occur in more than one individual. Analysis of urine, feces, hair or saliva for thallium contents should be done to confirm diagnosis, to assess the extent of thallium exposure and to monitor the response to treatment. Late diagnosis diminishes the effectiveness of treatment and increases the likelihood of permanent residual effects. However, prognosis is unpredictable: careful clinical assessments and instrumental findings may document a gradual improvement, which may continue for several years.

99. Brain 99MTC-HMPAO SPET and Neuropsychological Testing in Carbon Monoxide Acutely Poisoned Patients

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Objective: To evaluate CNS abnormalities due to acute CO poisoning. *Methods:* 40 patients without history of CNS disorder (male 14, female 26; mean age 30.85±11.9 years) treated at the Krakow Department of Clinical Toxicology in the heating season 2003/2004 were studied. COHb and blood lactate level (LA) were measured on admission. Neuropsychological tests of higher cognitive functions (Letter and Category Fluency, Complex Rey Figure, Auditory Verbal Learning and mental arithmetic tests) were performed during the acute stage of intoxication. The amalgamated results of all the tests were used in grading CNS dysfunction: 1—minor dysfunction; 2—moderate dysfunction; 3—signs of evident organic pathology. Brain 99mTc-HmPAO SPET was performed on 1–3 day post admission using double head Siemens gamma camera ICAM equipped with low energy high resolution collimators. 740MBq 99mTc-HmPAO was administered iv. The changes in regional cerebral blood flow (rCBF) were graded as follow: 1—minor hypoperfusion; 2—moderate hypoperfusion; 3—severe (diffuse) hypoperfusion. *Results:* The mean COHb level was 25.1±6.01%; LA concentration was 3.76±2.77 mmol/L; duration of exposure ranged from 10 to 180 min (38.2±42.9). In 70% of patients a degree of impairment in higher cognitive function (mostly grade 1 and a few grade 2) was found on neuropsychological testing. The tests results (percentile scores) were related to the norm for a Polish population. Neuropsychological profiles (for each the patient) obtained from the amalgamated results was used to calculate an overall score. Signs of organic CNS pathology were found in only one patient. Cerebral hypoperfusion was found in 72.5% (31/40) of 99mTc-HmPAO scans. None of our patients had focally decreased tracer uptake. A minor (37.5%) followed by moderate (25%) rCBF was found to be decreased to a minor (37.5% of cases) or moderate (25% of cases) degree. Severe hypoperfusion was observed in 6 (15%) of patients. The biggest changes were observed in the frontal cortex (72.5% of cases), basal ganglia (52.5%) and parietal cortex (47.5%). The highest percentage of asymmetry was found in the basal ganglia. *Conclusion:* We found a decreased rCBF in the acute stage of CO poisoning occurring mostly in the frontalor parietal cortex and basal ganglia. The results of 99mTc-HmPAO brain scintigraphy confirmed the potential of this method in early diagnosis of CNS dysfunction due to CO neurotoxicity. The lowered scores on neuropsychological tests in the majority of the patients also confirmed that acute

exposure to CO results in impairment of higher cognitive function. Further studies are needed to relate these acute changes to any longer term neuropsychological effects.

100. Methanol Poisoning: Multicentre Study of 32 Cases

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Objective: Within the frame of a collaborative program developed by the Health Ministry and the section of Clinical Toxicology of the Spanish Association of Toxicology since 1999 we have studied the cases of methanol poisoning treated in the Emergency Departments of Spanish Hospitals participating in the program. *Methods:* Data are submitted by members of the staff of the emergency department of the hospitals involved in the study. The clinical data for each patient include: sex, age, symptoms, treatment and outcome and product identification, exposure cause, location of exposure and exposure route. *Results:* We present the main characteristics of the 32 cases of methanol poisoning reported by 9 out of the 20 participating hospitals in 5 years. Mean age is 43 years. Males represent 62.5% and females 34.4%. The reason for exposure as domestic accident in 14 cases, suicidal in 11 cases, occupational 5 and unknown in 2 cases. The route of exposure was oral in 30 cases and cutaneous in 2 cases. 25 cases had some symptoms: neurological 14, respiratory 5, digestive 10 and cardiovascular 2 cases. A severe metabolic acidosis (pH<7.2) was reported in 5 cases. Some treatment was given in 30 cases: gastric decontamination in 6, cutaneous decontamination in 2, antidotes in 22 (ethanol 21 and fomepizole 1 case), hemodialysis in 7 cases and symptomatic measures in 30 cases. The time between exposure and hospital admission varied between 2 hours and 13 days. There were 5 deaths (15.6%), 4 suicidal and 1 domestic accident. Most of the non lethal cases had a good outcome but in 5 cases a visual sequel followed (blindness in 3 cases and some visual loss in 2 cases). *Conclusion:* Though methanol poisoning is not a frequent toxic case in the Spanish Emergency Departments it must be considered a dangerous kind of event since its mortality is much higher than in the general toxic cases, and the severity of the sequelae. Methanol poisoning affects an older population in comparison with the general toxic cases. The main reason for exposure is domestic accident closely followed by suicidal cases. Measures should be adopted to inform the population about the risks of this substance that is sold in Spain as a household cleaner and combustible alcohol.

101. Comparative Evaluation of Laboratory Diagnostics of Acute Alcohol Poisonings in Bulgaria—Preliminary Results

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Objective: The aim of our study was to compare the results of the different laboratory methods for the evaluation of blood ethanol levels and their clinical impact. *Methods:* We present 150 cases of patients admitted to the Toxicology Clinic with acute alcohol intoxication. A chemical toxicological blood analysis for estimation of precise concentration of blood ethanol has been carried out for each patient. The analyses have been done at the Chemical Laboratory of the Toxicology Clinic using two methods in parallel—gas-chromatographic ''headspace'' method with capillary column and flame ionization detector (FID), and iodometric ''Widmark'' micromethod. *Results:* In Bulgaria the iodometric ''Widmark'' micromethod for evaluation of grading of alcohol intoxications has been widely used up to now. We performed the two methods in parallel with the aim of reevaluating the accepted standard for classification of acute alcohol poisonings. Our results showed: in the group of patients with an ethanol level of 0.35 to 3.00 mg/ml the values of blood ethanol levels were comparable and the Widmark method gave values within the limits of admissible error (±0.20 mg/ml); in the group of patients with blood ethanol concentration below 0.35 or above 3.00 mg/ml remarkable differences in the blood ethanol levels determined by each method arose. These differences in many of the cases significantly exceeded the maximal admissible error of the Widmark method (±0.20 mg/ml). *Conclusions:* These results necessitate reevaluation of the accepted grading of alcohol poisonings and preparation of final criteria for determining the severity of acute alcohol poisonings.

102. Lipid Embolism and Acute Respiratory Distress Syndrome from Breast Injections of Mineral Oil

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Objective: Fat embolism, usually a result of long bone fractures, pancreatitis, or fatty liver, can result in deposition of lipid particles in pulmonary capillaries. Subsequent capillary destruction results in pulmonary shunting which then may lead to acute respiratory distress syndrome (ARDS). Lipid embolism as a result of exogenous injection of oil can be expected to result in similar consequences. In contrast, lipoid pneumonia occurs after oil aspiration and results in disruption of the capillary-alveolar interface. Lipoid pneumonia generally causes a pulmonary infiltrate on chest X ray (CXR) and symptoms of acute or chronic lung disease. We will describe a case of lipoid embolism and ARDS secondary to oil injection. *Case Report:* This is a case report of a 25 year-old transgender male who injected mineral oil for breast augmentation. After experiencing one day of chest pain, acute shortness of breath, and hemoptysis, the patient presented to the emergency department (ED) in acute respiratory distress. The CXR showed airspace consolidation, pneumomediastinum, and pneumopericardium. The patient was treated with oxygen, antibiotics, and corticosteroids. Subsequent bronchoalveolar lavage revealed lipoid pneumonia and secondary ARDS with alveolar hemorrhage. He recovered completely and was discharged from the hospital after 11 days. *Conclusion:* This is the only case report the authors are aware of which describes lipid embolism and ARDS as a result of subcutaneous mineral oil injections. Providers should be aware of potential complications of non-traditional methods of gender transformation.

103. Deaths Due to Methanol Poisoning Remain High in Finland

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Objective: Previously we have reported sudden increase of both fatal methanol poisonings and inquiries to FPIC concerning methanol after 1995. The increase followed the entry of Finland to EU and consequent harmonisation of laws and regulations resulting in abolishment of restrictions concerning the retailing of methanol. Windshield washer fluids containing methanol appeared on the market and fatal poisonings increased among chronic alcoholics. In July 2000 new more stringent regulations concerning toxic classification of methanol were introduced. The aim of this study was to find out how the situation has developed in the last 5 years. *Methods:* We studied the statistics of causes of death in Finland and the number of inquiries to our Poison Information Centre (FPIC) concerning methanol for the years 1992–2003. The causes of deaths were verified by forensic analyses. *Results:* As our previous report concerning 1988–1998 showed, deaths due to acute methanol poisoning increased after 1995. The number of deaths peaked in 2000, the same year the tighter regulations were introduced. Since then the number of deaths has decreased only slightly, and has remained more than twice as high as it was before 1995. All but a few of the deaths were among chronic alcoholics using methanol as surrogate for alcohol due to its low price. *Conclusion:* Use of methanol containing car chemicals as surrogate for alcohol remains a problem in Finland. More stringent regulations on the sale of methanol containing products may be needed. Other causes for methanol poisonings remain rare.

TABLE 1
Deaths caused by methanol and inquiries to the FPIC in Finland during 1992–2003

	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003
Deaths	1	5	2	8	15	18	29	33	46	30	25	43
Inquiries	14	37	12	45	37	50	47	68	–	84	122	61
% of total	0,05	0,12	0,05	0,15	0,12	0,14	0,13	0,18	–	0,22	0,32	0,15

104. Severe Ethylene Glycol Ingestion Complicated by Refractory Acidosis and Death

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Objective: The availability of antidote therapy for ethylene glycol makes serious poisonings rare; the fatality rate after ingestion is one percent. We report a case of a severe intoxication that was unresponsive to traditional antidotes. *Case Report:* A 47-year-old man ingested an unknown amount of ethylene glycol in a suicide attempt. He was found to be unresponsive eleven hours after the ingestion, and was taken to the hospital. Initial laboratory data revealed an anion gap of 32 and an osmole gap of 55. Assays for acetaminophen, salicylate and ethanol were negative. A profound metabolic acidosis was present [pH 6.96/pCO_2 28 mm Hg/pO_2 296 mm Hg/(calculated CO_2 6 mmol/L)/100% saturation on 100% FiO_2]. The patient was intubated, and treatment with fomepizole and hemodialysis (with a bicarbonate dialysate) was initiated within one hour of admission to the intensive care unit. While in the intensive care unit, the patient developed hypotension and required increased ventilatory support. An echocardiogram was performed which showed no evidence of cardiac ischemia. Progressive acute lung injury developed with a subsequent ABG on 100% FiO_2 of 6.8/62/68/(10)/78%. The patient became more difficult to ventilate, and the acidosis remained refractory to dialysis and attempts at hyperventilation in the face of normal hemodynamics. He expired eighteen hours after the ingestion occurred. A serum ethylene glycol level drawn one hour before the patient's death was 183 mg/dL; a methanol level drawn at the same time was nondetectable. *Discussion:* Fomepizole and hemodialysis are generally effective in correcting the metabolic acidosis associated with ethylene glycol metabolism. This patient developed acute lung injury as a complication of his ingestion; ventilation became difficult due to decreased pulmonary compliance. He developed respiratory acidosis that, along with the co-existing metabolic acidosis, was refractory to treatment with hemodialysis and fomepizole. Due to the multi-system involvement seen with severe ethylene glycol intoxication, extreme measures of treatment such as cardiopulmonary bypass are likely to be of limited utility and were not utilized in this case. *Conclusion:* Physicians must be aware of the potential for ethylene glycol to cause acidosis that may be refractory to all standard treatments. *References:* Catchings TT, Beamer WC, Lundy L, et al. Adult respiratory distress syndrome secondary to ethylene glycol intoxication. *Ann Emerg Med* 1985; 14(6):594–596. Gardner TB, Manning HL, Beelen AP, et al. Ethylene glycol toxicity associated with ischemia, perforation, and colonic oxalate crystal deposition. *J Clin Gastroenterol* 2004; 38(5):435–439. Rasic S, Cengic M, Golemac S, et al. Acute renal insufficiency after poisoning with ethylene glycol. *Nephron* 1999; 81:111–120.

105. Ethylene Glycol Poisoning: Different Course in Suicidal and Non-Intentional Ingestions

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Objective: To compare severity of intoxications in suicidal attempts with non-intentional ingestion. The estimated lethal dose of ethylene glycol (EG) of 100 ml is easily attained in overdose. *Methods:* Data about the clinical course of EG poisonings reported to the Czech Toxicological Information Centre in the years 2000–2002 were analysed. Data as obtained from discharge records from the hospital, and if available from toxicological analyses. The χ-square test, Student's t-test, Fisher's test and calculation of linear correlation coefficient were used for statistical analysis. The significance level was set at 0.05. *Results:* From a total 188 calls concerning EG, 33 discharge records were obtained. These were from 30 males (age 5–74 years) and 3 females (age 10–54 years). Ingested dose correlated with kidney damage, level of metabolic acidosis (pH) and depression of central nervous system. The time interval between ingestion and admission correlated with metabolic acidosis, severity of symptoms and length of hospitalisation. 91% of the patients were treated with ethanol, 61% were treated with haemodialysis (HD). Eleven patients were suicide attempts. They ingested significantly higher dose of EG (mean 361 ml, range 100–1000 ml), than patients who drank EG by mistake. Median latency was 7 hours (3–24 hours), mean EG in blood 2.3 g/l. Four patients had substantially increased laboratory markers of nephrotoxicity, four increased markers of hepatotoxicity. Nine patients were treated with HD, one died (dose unknown). Ingestion of 10 fold lethal dose was survived. Reason of ingestion remained unknown in eight patients. Very probably their ingestion was also intentional. In five patients the time of ingestion was unknown. Dose was known in three patients (150, 300 and 800 ml). EG in blood was measured in three other patients (0.6, 2.1, and 8 g/l). Five patients had elevated laboratory markers of nephrotoxicity, four of hepatotoxicity. Six patients were treated with HD; one died (dose unknown). Fourteen patients ingested EG by mistake. Mean reported dose was 71 ml (30–200 ml), median latency one hour (0.5–72 hours), mean EG in blood 0.4 g/l. Four patients had mildly increased laboratory markers of nephrotoxicity, two of

hepatotoxicity. Six patients were treated with HD (only 3 fulfilled criteria for HD). Their laboratory values normalised. One 74-years old man died (dose unknown, pre-existing chronic renal failure). *Conclusion:* In patients, who ingested ethylene glycol by mistake, significantly lower dose was ingested, and significantly shorter time-interval between ingestion and presentation was seen than in other patients. The course of intoxication and the outcome was favourable in all but one patient who had pre-existing chronic renal failure. Acknowledgement: Supported by MSM J13/98 111100002.

106. Ethyl-Parathion is Still a Cause of Serious Poisoning in Europe—A Case Series of Three

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Background: In Denmark the organic phosphorus compound ethyl-parathion was withdrawn from the market in 1990, as it has been in other European countries during the last decade. Since September 2003 it has been prohibited in the EU. Ethyl-parathion, an insecticide, was previously quite often used for suicide attempts. The success rate was high. The cause of death is mainly cholinergic excess. We report three recent cases following intentional ingestion. *Case 1:* A-56-year old man was found drowsy and perspiring with excessive salivary secretion, slurred speech and foaming at the mouth approximately 15 minutes after ingestion of ethyl-parathion, which the family had kept for years in their tool shed. He soon developed vomiting, diarrhoea, respiratory depression with bronchial hypersecretion and convulsions. In the ambulance he became bradycardic with two short self-limiting episodes of asystole. Following admission he was intubated, aspirated and treated with activated charcoal, atropine and obidoxime. Arterial puncture showed severe combined metabolic and respiratory acidosis with pH 6.92; pCO_2 11.6 kPa; BE-18.4. P-amylase was greatly elevated (5673 U/l). Over the following two days he had bronchial hypersecretion, excessive salivation, hypotension, intermittent 2nd degree AV-block and progressive pulmonary oedema. He was treated with large and frequent doses of atropine and symptomatically with dopamine. He continued to be comatose without voluntary movement and developed multi-organ failure as well as central failure of the regulation of temperature compatible with anoxic brain damage following the initial respiratory and circulatory collapse. He died three days after admission. *Cases 2 and 3:* An elderly married couple was found in their home approximately eight hours after drinking ethyl-parathion. The husband was dead at the time of discovery. The 75-year-old woman was admitted to the emergency department. She was initially somnolent and confused, but was able to tell what had happened. She was treated with activated charcoal. Over the next 24 hours she developed fasciculations, had a fluctuating state of consciousness and developed an aspiration pneumonia demanding mechanical ventilation. She was treated with atropine infusion and obidoxime was administered several times. She survived, but has complete amnesia also concerning the death of her husband. *Conclusion:* Poisonings by ethyl-parathion result in loss of consciousness, coma, respiratory depression, cardiac dysrhythmias and bronchial hypersecretion and can be fatal. Ethyl-parathion was widely available and though prohibited now, we still see this serious poisoning. We need to be reminded of the symptomatology to be able to recognize and treat these patients appropriately.

107. Carbon Monoxide Poisoning: Do We Miss Some of Them in the ED?

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Objectives: Carbon monoxide is a colorless, tasteless, odorless and non irritating gas (1). It is a preventable cause of morbidity and mortality, and is responsible for many cases of non-fatal unintentional Carbon Monoxide (CO) poisoning (2). As carbon monoxide poisoning results in diffuse tissue hypoxia normobaric or hyperbaric oxygen therapy is an essential component of therapy (3). *Methods:* We retrospectively evaluated the charts of patients admitted to Gazi University Hospital Emergency Department with carbon monoxide poisoning between 01.01.02 and 30.08.04. We reviewed the forms of 323 patients with CO poisoning and the following data were recorded: patient's age, gender, route of poisoning, hour of admission to the Emergency Department (ED), complaints, vital signs, physicial findings, laboratory findings and hyperbaric oxygen therapy. *Results:* 323 patients were evaluated. 115 (36%) of the patients were male and 208 (64%) were female. The mean age was 29.36±17.24. 114 (37%) of the patients came to the ED between 18.00–24.00 hours. All of the patients were exposed to carbon monoxide accidentally. The most common sources of poisoning were stove (29%) and water heater (24%). The frequency of complaints

was as follows; headache 55%, dizziness in 43%, syncope in 28%, palpitation in 13%, seizure in 4%, nausea in 49% and dyspnea in 5%. Abnormal vital signs included: hypotension in 14%, hypertension in 7%, tachycardia in 47% and tachypnea in 79%. Mean carboxyhemoglobin value was 26.31 ± 11.52. No statistically significant relationship was found between pO_2 and COHB levels (t-test, $p=0.179$). Syncope was most commonly seen among patients having CoHb levels of ≥ 30. Syncope occured more frequently in patients with high COHB levels (χ^2, $p<0.001$). Syncope was seen more common among females (χ^2, $p=0.003$). Most patients were admitted to the ED from December through March. 272 (84%) of the patients were discharged, 28 (8%) were interned to services. 287 (89%) patients didn't take hyperbaric oxygen therapy. 34 (11%) patients had taken hyperbaric oxygen therapy. *Conclusion:* Carbon Monoxide poisoning was seen during the winter months and exposure was accidental. Serious symptoms were seen among patients having increased CoHb levels. Syncope was most commonly seen among patients having COHB levels of ≥ 30. Emergency Physicians must be suspicious during winter months and education of public about Carbon Monoxide poisoning must be the main goal of healthcare providers.

108. Serum Nitric Oxide Concentration in Carbon Monoxide Acutely Poisoned Patients Considering a Smoking Habit

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Objective: The important role of Nitric Oxide (NO) in relaxing vascular smooth muscle is well known. The aim of this pilot study was to asses the impact of cigarette smoking on NO serum concentration in acutely CO poisoned patients. *Methods:* The study group included 16 males and 8 females (age: 16–71 years) treated at the Kraków Department of Clinical Toxicology because of acute CO poisoning (mean COHb 28.81 ± 9.17, range—14.9–58.8%). They were not suffering from any concurrent disease and were not on any medications, including vitamins, before CO intoxication. The study group consisted of 9 smokers and 15 non-smokers. The control group included 19 females and 10 males with an average age of 37.17 ± 13.29 (10 smokers and 19 non-smokers) who were not CO intoxicated. The measured marker of cigarette smoking was urinary cotinine. The blood samples for NO measurement were withdrawn into vacutainer tubes and centrifuged to separate the serum. An aliquot of serum was than removed and stored at $-80^{\circ}C$. A commercially available kit (Nitric Oxide Colorimetric Assay (Roche Diagnostics GmbH) was used. NO was detected via nitrite. The nitrate present in the samples was reduced to nitrite by NADPH in the presence of the enzyme nitrate reductase. The nitrite formed reacted with sulphanilamide and N-(1-naphtyl)-ethylenediamine dihydrochloride to give a red-violet diazo dye. The diazo dye was measured on the basis of its absorbance in the visible range at 550 nm. 24-hour blood pressure monitoring with Holter monitoring was performed. *Results:* The highest NO (μM) concentration ($df=3$; $F=3.507$; $p=0.022$) and lowest diastolic blood pressure were noted in the subgroup of CO acutely poisoned smokers. Diastolic blood pressure in the control (not CO poisoned) nonsmoker subgroup was higher compared to acutely CO poisoned (both smokers and nonsmokers) and also to the control subgroup exposed only to CO from a cigarette smoke. *Conclusion:* Serum NO concentration was increased in smokers compared to nonsmokers in both CO poisoned and control groups, but in the subgroup of CO acutely poisoned patients who were active cigarette smokers the elevation was highest. In CO poisoned smokers the lowest diastolic blood pressure was noted.

109. Features of Acute Ethanol Poisoning of Children

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Objectives: Data from the paediatric poisoning treatment centres in Moscow, Omsk, Irkutsk and Voronezh suggest that the number of cases of acute ethanol poisoning in children is increasing. They account for 12 to 16% of all hospitalized patients with exogenous intoxications. Acute ethanol poisoning is common in children of various ages, but the risk group is schoolchildren aged from 7 to 15 years. The aim of the study was to identify the concentration thresholds for key clinical syndromes of ethanol poisoning in children. *Methods:* The ethanol concentration in blood was measured by gas liquid chromatography and matched

against clinical features. *Results:* The observation group totalled 47 Russian children aged from 7 to 15 years. It was found that at ethanol concentrations from 0.4 to 2.0 g/L children usually remained conscious. Coma was reported at ethanol concentrations from 2.0 to 5.4 g/L. Poisoning of moderate severity (0.9 to 1.9 g/L) was accompanied by apathy and, less frequently, psychoactive agitation, reduced muscle tone and tendon reflexes. Skin colour was normal or pale. Arterial pressure remained unchanged in 70% of cases but was reduced in 30% of patients. The most common ECG findings were rhythm disturbances manifested by sinus brady- and tachycardia, and signs of variably expressed metabolic changes. All children with severe ethanol poisoning in the resorption stage (1.64 to 5.4 g/L) had a considerably depressed level of consciousness, with reduced muscle tone and tendon reflexes. Deep coma (2.0 to 5.4 g/L) was accompanied by loss of sensitivity to pain, a sharp reduction in pupillary and tendon reflexes, muscular hypotonia and hypothermia. Several patients developed acrocyanosis (2.6 to 5.4 g/L) and marble skin (4.2 to 5.4 g/L). Patients in deep coma had central respiratory failure (above 3.8 g/L). Patients had variable haemodynamics: 80% of cases showed hyperkinetic changes, 20% had decreased cardiac output. This group of patients had arterial hypotonia (1.9 to 5.4 g/L) and tachycardia (1.0 to 5.4 g/L). On ECG there were signs of reduced intrasystolic conductivity with 1-st degree atrioventricular block and, rarely, transitory prolongation of the Q-T interval. There were no lethal cases. *Conclusion:* Ethanol concentrations at which poisoning signs appeared in children were extremely variable from 0.4 g/L to 5.4 g/L. However at ethanol concentrations exceeding 2 g/L one could expect deep coma characterized by reduced reflexes, hypothermia, respiratory deficiency and cardio-vascular disturbances. These changes required emergency corrective measures.

110. Liver Transplantation for Acute Cholestatic Hepatitis After Herbal Tea Use

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Introduction: The use of herbal preparations for treatment of diseases is increasing in popularity in Europe and North America. At the same time an increase of acute hepatitis induced by herbal products has been observed, in particular with *Piper methysticum* (kava kava) preparation. We present a case report with liver transplantation for acute cholestatic hepatitis after multiple herbal tea use. *Case Report:* A 48 year old woman, in good health, was advised by her hairdresser to use some herbal teas, prepared by a self-defined 'herbal scientist', for the treatment of gastric pyrosis lasting for a few weeks. The first preparation, used for four days, was the Indian Herbal Tea (*Arctium*, *Rumex acetosa*, *Ulmus fulva*, *Rheum officinalis*, *Plantago lanceolata*, *Trifolium pratense* and *Fraxinus*). Within one week the patient observed dark urine, but she started the other preparations (*Achillea* and *Calendula*, colloidal silver and the Swedish Herbal Bitter with *Aloe*, *Commiphora*, *Cinnamomum cassia*, *Rheum officinalis*, *Angelica* and camphor). Only *Aloe*, *Cinnamomum cassia* and *Trifolium pratense* are known hepatotoxic plants. After 10 days jaundice was evident and she was admitted to our hospital. The laboratory controls showed increase of transaminases (ALT 1,442—AST 1,043) and hyperbilirubinemia (total 4.8, direct 3.5 mg/dL), elevated alcaline phosphastase (201 U/L) and LDH (1,533 U/L) and C-reactive protein increase (12 mg/dL). In the following weeks she developed a severe cholestatic hepatic failure: hyperbilirubinemia (total 28.4, direct 19.9 mg/dL), prolonged PT-INR (2.25) and APTT-R (1.68), hyperglycemia (190 mg/dL), hyperammoniemia (120 mcMol/L) with confusional state. Viral and autoimmune hepatitis were excluded and liver biopsy confirmed toxic cholestasis with cholangitis and biliar metaplasia. After liver transplantation, the patient was discharged in good condition. *Conclusion:* In case of toxic acute hepatitis, toxicologists must verify whether herbal preparation have been used.

111. Some Epidemiological and Clinical Data from Loxosceles Spider Bite—Unicamp Poison Center, Brazil, 1988–2004

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Objective: To present some epidemiological data of patients treated at the UNICAMP University Hospital (UH) for suspected Loxosceles spider bites, and 2 cases with serious complications. *Methods:* A retrospective case series of patients at the UH. Our study group comprised 48 patients from 1988 to 2004, with suspected Loxosceles spider bites treated, and 2 cases with serious complications. We have photos from some cases. Our institution is a referral center for our area. *Cases Series:* The mean age of our 48 patients 20.86 years (range, 4 days to 73 years), 27 adults and 21 children. The mean time from the supposed accident to the initial presentation at the UH, for 43 patients was 2.92 days, being 2.2 for children and 3.44 for adults (excluded case 1). Half of the patients (24 from 48) were treated with antibiotics, 4 with Dapsone and 28 (58.33%) with antiarachnidic serum (polivalent serum) and 9 (18.75%) with antiloxoscelic serum (both from Butantã Institute). Case 1) A 51-year-old diabetic farmer arrived at

the Orthopedic Department of the UH after being bitten by a spider on the junction of middle and the distal anterior third of the right forearm 3 months earlier. After the bite, erythema, edema, purple spots developed on the region and spread to the posterior part of the limb, with necrosis. He only sought medical care 8 days after the accident. Although being treated with several antibiotics and submitted to 3 surgical debridements, the lesions worsened, with necrosis of a large part of the soft tissue of the forearm, with bone protrusion. At the UH, after a week of treatment for sepsis, diabetes and hyponatremia, he was submitted to amputation at the proximal third of the forearm. Case 2) A 30-year−old, man was bitten in the shoulder region by a spider, developing a local 4 cm diameter ulcer. On the 4th day, he began to present weakness, malaise, fever, headache and palor. On the 6th day, he arrived at the UH, with severe anemia (Hb=3.8 g%), jaundice (total bilirubin=6.1, direct=0.4, indirect=5.7, hemoglobinuria (++++), myoglobinuria (−) and despenia). He received 5 vials of antiarachnidic serum, being given 4 units of blood and hydration. He didn't develop renal failure, and was released after 7 days. *Comment:* As our institution is a referral center for our area, this makes it likely that we see the worst bite cases in the region. The diagnosis and treatment decisions are based on clinical diagnosis.

112. Plant Poisoning in the Slovak Republic

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Objective: Our Toxicological Information Centre (TIC) in Bratislava has received 16,546 inquires from all over Slovakia. Plant exposures represent 4% of all cases collected by TIC. *Methods:* Review of cases reported to the TIC in the years 1994—2003. *Results:* During the 10—years period 584 plant and herbal exposures were reported to the Slovak TIC.Adults corresponded to 19% and children to 81% (58% of them were less than 5 years old). Unintentional exposures were 79%, abuse 20,5%, suicidal attempt (0,34%). Ingestion was the route more usually involved (96% of cases); other routes were via mucous membrane contact (3,4%), dermal contact (0,34%) or ocular (0,2%). 59 different plant species were involved. The plants most frequently implicated in decreasing order were: *Datura stramonium* (160 cases), Dieffenbachia (50 cases), *Atropa belladonna* (33 cases), *Viscum album*, *Lonicera xylosteum*, *Mahonia aquifolium*, *Laburnum anagyroides*, *Convallaria majalis*, *Taxus baccata*. Of the total outcomes, clinical manifestations were: neurological (77,5%), gastrointestinal (9,5%), mucous membrane iritation (11,2%), dermal-ocular (1,7%). 80,2% of patients were asymptomatic, 16,5% of patients developed minor symptoms and 3% of patients developed moderate symptoms. One patient developed severe symptoms and 2 persons died (*Taxus baccata*, *Colchicum autumnale*). *Conclusions:* Accidental poisonings by *Colchicum autumnale* are due to mistakenly eating wild plants such as *Allium ursinum*. *Atropa belladonna* berries were confused with *Vaccinium myrtillus*. Most plant ingestions were not associated with the development of symptoms.

113. Poisoning by *Agauria salicifolia* (Grayanotoxin Containing Plant): A Case Report from Reunion Island

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Introduction: Plants of the Rhododendron genus are well known to contain grayanotoxins that can induce severe poisonings. The most frequent exposure concerns the ingestion of contaminated honey, but intoxication can occur after direct absorption of leaves or flowers. Other plants of the Ericaceae family are supposed to produce the same kind of toxins. *Agauria salicifolia* is a species close related from Rhododendron, endemic of Mascareigne Islands and which grows in volcano slope forests. *Case Report:* In Reunion Island (French territory in the Indian Ocean), a woman of 29 years old without previous history ingested a preparation of *Agauria salicifolia* leaves. It was a mistake as in the island, this plant is classically used for cutaneous applications (plaster for eczema treatment). Thirty minutes after the absorption, she had vomiting and diarrhoea, and she felt very weak. As the symptoms persisted during all the day, she decided to consult at the emergency unit where the practitioners observed the following clinical features: excessive perspiration, skin rash, arterial hypotension (6/4), bradycardia (40/min). She was managed in intensive care unit where she received fluids. She recovered in few hours without specific treatment. *Conclusion:* This case is the first recorded observation in the literature of intoxication due to direct ingestion of *Agauria salicifolia*, confirming that different genus of Ericaceae family can induce grayanotoxin poisonings.

114. Poisoning with *Amanita pantherina* and *Amanita muscaria*: Two Different Syndromes?

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Objective: Amanita pantherina and *Amanita muscaria* contain ibotenic acid and muscimol. Ibotenic acid is known to act on glutamic acid receptors in the central nervous system and has excitatory action. On the other hand, muscimol acts on GABA receptors and has depressant action. After ingestion ibotenic acid is metabolized to muscimol. *Amanita pantherina* contains less ibotenic acid and more muscimol compared to *Amanita muscaria*. The aim of our study was to compare the clinical picture in *Amanita pantherina* and *Amanita muscaria* poisoning. *Methods:* In a retrospective study we evaluated the clinical picture of patients poisoned with *Amanita pantherina* and *Amanita muscaria* who were hospitalized in our Poison Control Center (PCC) during the last 20 years. *Amanita muscaria* and *Amanita pantherina* ingestions were confirmed by a mycologist. Fisher exact test was used for categorical variables. A p value of less than 0.05 was considered as significant. *Results:* 13 patients poisoned with *Amanita muscaria* and 7 patients poisoned with *Amanita pantherina* were hospitalized in our PCC. 9 patients poisoned with *Amanita muscaria* picked up and ate a mushroom supposed to be *Amanita caesarea* and all 7 patients poisoned with *Amanita pantherina* picked up a mushroom supposed to be *Amanita rubescens*. Patients poisoned with *Amanita muscaria* were more often confused, agitated and had hallucinations and convulsions compared to the patients poisoned with *Amanita pantherina*, but these differences were not significant ($p>0.05$) (Table 1). On the other hand, patients poisoned with *Amanita pantherina* were significantly more commonly comatose ($p<0.05$) (Table 1). Cholinergic signs including lacrimation, salivation and sweating were present in six patients poisoned with *Amanita muscaria* and two patients poisoned with *Amanita pantherina* ($p>0.05$). Anticholinergic signs were not observed in our patients. Agitated patients were successfully treated with benzodiazapine. *Conclusion:* Loss of conciousness was significantly more common in *Amanita pantherina* than *Amanita muscaria* poisoning. This could be due to the smaller amount of excitatory ibotenic acid in *Amanita pantherina* compared to *Amanita muscaria*. Accordingly, so-called ibotenic syndrome after *Amanita muscaria* and *Amanita pantherina* poisoning could be divided into two subtypes, but the clinical importance of differentiation should be further evaluated. *Reference:* Michelot D, Melendez-Howell LM. *Amanita muscaria*: chemistry, biology, toxicology, and ethnomycology. *Mycol Res* 2003; 107:131–146.

TABLE 1
Symptoms and signs after *Amanita muscaria* and *Amanita pantherina* ingestion

	Amanita muscaria (n=13)	*Amanita pantherina* (n=7)	P value
Confusion	9	2	0.16
Agitation	6	1	0.32
Convulsion	4	1	0.61
Hallucinations	5	1	0.35
Coma	1	4	0.03

115. *Veratrum album* Poisoning Mistaken for *Gentiana lutea*

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Introduction: The root extract of yellow gentian, *Gentiana lutea*, is commonly used for flavoring different kinds of herbal ethanol-base bitter. Gentian is widely used in traditional medicine to promote upper digestive function and to stimulate the gallbladder and liver and also used in febrile illnesses, in treating gout and helminthiasis. The plant is very similar to white hellebore, *Veratrum album*, and often both grow in the same fields; it is easy to confuse them before they flower: the main characteristics for their botanic determination are leaves (alternate in *Veratrum album*, opposite in *Gentiana lutea*) and flowers (white for *Veratrum album*, yellow for *Gentiana lutea*). Protoveratrine A and B, germine, veratramine and jervine are the most important toxic alkaloids of *Veratrum album* which acts on the voltage-dependent sodium channel prolonging sodium current

influx, increases levels of excitatory amines and at high dose has a digoxin-like effect. *Case Report:* A 66-year-old 65-kg healthy man, while was walking on the mountain, collected and chewed some stems of plants that he believed to be *Gentiana lutea*. After less than one hour he showed severe vomiting, abdominal pain, dizziness and when the emergency medical service arrived by helicopter on the mountain found the man with severe hypotension (70/50 mm Hg blood pressure), bradycardia, right bundle branch block and aphasia. The patient was treated with normal saline and polygeline infusion, atropine and dopamine, gut decontamination and charcoal administration. Laboratory evaluation showed an increase of troponin I (4.0 ng/mL) but no miocardial infarction was observed. In a few hours the patient's symptoms resolved and he was discarged from the hospital after 48 hours. *Conclusion:* The difficulties for people without botanical preparation in distinguishing *Veratrum album* from *Gentiana lutea* can expose them to severe poisoning with potential evolution to death and only an immediate and aggressive treatment can save the life of the poisoned patient.

116. *Amanita phalloides* Poisoning During the Third Trimester of Pregnancy

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Objective: Amanita phalloides poisoning in pregnancy is rare so every individual observation is of great importance. We report a case in the 36th week of pregnancy. *Case Report:* A couple, who immigrated from Kasachstan, ingested wild mushrooms they had collected themselves. Four hours after ingestion both began to suffer from vomiting and diarrhoea. Approximately 7 hours after ingestion gastric lavage was performed. *Amanita phalloides* was identified in the gastric content by an expert. Clinical management consisted of gut lavage, multiple doses of activated charcoal, penicillin, silymarin and acetylcysteine. 24 hours after ingestion the patient's AST an ALT began to rise and quick time and factor V activity decreased to 55% and 19% respectively. As the further course couldn't be predicted and in order to prepare the woman for a liver coma therapy and/or liver transplantation a ceserean section was performed. Prophylacticly the patient received 6 fresh frozen plasma and two packed red cells intra- and postoperative. The child's liver tests after delivery were always normal. It only suffered from an IRDS (infant respiratory distress syndrome) because it wasn't given betamethasone for acceleration of lung maturation. Two days after ingestion the womans ALT and AST reached their maximum values (AST 1351 U/L, ALT 1952 U/L) and quick time (51%) and factor V activity (24%) showed their nadir. *Conclusion:* There are only few (about 20) case reports on *amanita* poisoning during different stages of pregnancy in literature. All but one observed that even when a maternal liver damage is seen the fetal liver doesn't seem to be involved in the poisoning. In one case involving a medium grade poisoning in the first semester in 1978, the pregnancy was terminated by injecting prostaglandin F2α retro-amniotically. Autopsy and histology showed fetal liver injury which was attributed to a possible amatoxin effect. This is indeed the only report of toxic effects on the fetus. Our case supports the assumption that amatoxin doesn't cross the placental barrier. In case of a beginning severe liver damage and strong coagulation abnormalities at the end of pregnancy it is necessary to discuss the need and the time for a preterm delivery.

117. Life-Threatening Complications in Black Widow Spider Envenomation

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Objective: Black widow spider envenomation could be life threatening and is a rare in our clinical practice. The aim of this report is to present three cases of poisoning with Black widow spider's venom (*Latrodectus mactans tredecimguttatus*) which evolved in different complications. *Case Series:* The presentation of latrodectism (grade 3 at admission—Clark classification) was noted in a 70-year shepherd, a 43-year female farmer and a 34-year male tobacco farmer. All of the patients developed ''target lesion.'' Within a one-hour period they presented with excessive diaphoresis, a hypertoxic myopathic syndrome with painful cramps and restlessness, ''facies latrodectismica,'' different autonomic-vegetative effects and life-threatening complications such as extreme hypertension (2 patients) and acute pulmonary toxic oedema (1 patient). Laboratory analyses revealed leukocytosis with neutrophilia, hyperglycemia, moderately increased aspartate aminotransferase, lactate dehydrogenase

TABLE 1
Laboratory findings at admission and during hospitalization

	I pt				**II** pt				**III** pt			
Lab/d Hosp	I	II	III	K	I	II	III	XI	I	II	III	V
Le × 10	13.5	15.4	12.3	8.5	30.5	26.3	27.7	9.4	17.7	14.2	9.7	6.9
Ne (%)	90	91	89	66	87	94	76	66	91	83	69	60
G mmol/l)	9.1	8.0	4.9	5.6	13.5	9.8	6.7	5.7	11.2	7.3	3.8	4.2
CPK(U/l)	/	69	120	70	55	487	390	85	208	397	143	98
LDH(U/l)	/	601	510	266	529	837	623	295	245	292	236	229
AST(U/l)	/	69	120	38	82	62	51	28	91	72	56	41

Lab.f—laboratory findings, d. hosp-days of hospitalization, I-first patient, II-second patient, III-third patient, pt-patient, Le—leukocytes in blood, Ne—neutrophilia in blood, G—glycemia(s) CPK—creatinin phosphocinase, LDH—lactate dehidrogenase, AST—aspartate aminotransferase, LDH—lactate dehydrogenase, K—control check after one month.

and creatinin phosphokinase (Table 1). Treatment included local wound care, muscle relaxants, opioids, Ca-gluconate, antihypertensive therapy (ACE-inhibitors), and high doses of methylprednisolone (1600 mg) and adrenaline in the patient with acute pulmonary toxic edema. No Latrodectus antivenin was used. Pain relief was noted after an average of 52 hours after admission. Patients were discharged after an average of 9.3 days. *Conclusion:* Because of marked autonomic and neurotoxic effects of alfa-latrotoxin, latrodectism may be presented with various, sometimes life-threatening complications. Capturing a specimen of *L.m.tredecimguttatus* at our territory for the first time convinced us to think about these envenomations more often in our practice. *Reference:* Clark RF, Wethern-Kestner S, Vance MV, et al. Clinical presentation and treatment of black widow spider envenomation: review of 163 cases. *Ann Emerg Med* 1992; 21(7):782–787.

118. Recurrent Ciguatera Symptoms Nine Years After Initial Poisoning

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Objective: Patients with a prior history of ciguatera have developed typical ciguatera symptoms after the ingestion of various food sources. We report a patient who developed recurrent ciguatera symptoms after eating chicken. *Case Report:* A 32-year-old woman was diagnosed with ciguatera after consuming barracuda while vacationing on the Caribbean island of St. Martin. Her initial symptoms lasted less than one month, and included nausea, vomiting, perioral paresthesias and reversal of hot and cold sensations. Nine years later, the patient developed perioral paresthesias and right-sided facial numbness after eating chicken at her home in Connecticut. Other family members who shared the same meal were asymptomatic. The patient's symptoms were similar to those she experienced when she was initially diagnosed with ciguatera, and resolved slowly over a period of weeks. *Discussion:* Ciguatera is the most common fish-borne disease in the world, and is characterized by acute gastrointestinal, cardiac, and neurologic symptoms. After the initial manifestations subside, there is no immunity and recurrence of illness is possible. While the acute manifestations of ciguatera are well described, recurrent symptoms are less widely reported. Sensitization, in which people with a history of ciguatera develop recurrent symptoms after eating fish that did not cause symptoms in others, may occur months to years after the initial illness. Sensitization has also been reported after the ingestion of alcohol and protein-rich foods. The etiology of this phenomenon is unclear; immunologic, allergic, and hypersensitivity reactions have been hypothesized as the reason for the development of recurrent ciguatera symptoms. Additionally, animal feed may include fish meal that contains subclinical levels of ciguatoxins. Sensitization to these small levels of toxins may produce recurrent symptoms in humans who consume fish meal-fed animals. *Conclusion:* Physicians should be aware of the potential for ciguatera to recur, and the diagnosis should be suspected in any patients with symptoms reminiscent of their initial presentation. *References:* Bagnis R, Kuberski T, Laugier S. Clinical observations on 3,009 cases of ciguatera. *Am J Trop Med Hyg* 1979; 28(6):1067–1073. Gillespie NC, Lewis RJ, Pearn JH, et al. Ciguatera in Australia: occurrence, clinical features, pathophysiology and management. *Med J Aust* 1986; 145:584–590. Lewis RJ, Ruff TA. Ciguatera: ecological, clinical and

socioeconomic perspectives. *Crit Rev Environ Sci Tech* 1993; 23(2):137–156. Pearn J. Neurology of ciguatera. *J Neurol Neurosurg Psychiatr* 2001; 70:4–8.

119. Hypoglycemia After *Allium cepa* Sprouts Ingestion

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Introduction: The bulb of onion, *Allium cepa*, is commonly used in meals all over the world. Hypocholesterolemic, fibrinolytic, inhibition of thrombocyte aggregation, fatty acid oxygenases and antiasthmatic properties have been described and used in traditional medicine. A diethyl ether extract from onion has been shown to contain diphenylamine which causes hypoglycemic effects in animals (1,2). *Case Report:* A 63-year-old 75 kg healthy man was admitted to the emergency department for sweating, nausea, epigastric pain and pyrosis, dizziness and severe hypoglycemia (50 mg/dL) one hour after the ingestion of a huge amount of onions' sprouts salad with cheese. The patient was treated immediately with 3 grams of hypertonic glucose solution and the symptoms resolved promptly. Laboratory evaluation was normal except the hypoglycemia. Other causes of hypoglycemia were excluded (in particular hyperinsulinemia) and no hypoglycemic episodes were observed in the patient in the following months. The probable correlation of the hypoglycemia with the *Allium cepa* ingestion remains the only hypothesis for the cause of the event. *Conclusion:* Rare and very strange case reports about the effect of plants on human health can find a probable correlation only if experimental studies on animals have been published before, and only after the complete exclusion of other causes. *References:* 1. Salveron MJ, Cantoria MC. Studies on the extracts of two Philipine-grown cultivars of *Allium cepa*. *Planta Medica* 1989; 55:662. 2. Jain RC, Vyas CR. Hypoglycaemia action of onion on rabbits (letter). *Br Med J* 1974; 2(921):730.

120. Accidents Caused by Coral Snakes (*Micrurus spp.*) in Campinas, São Paulo, Brazil

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Objective: To report a retrospective study of coral snake bites. *Case Series:* From May 1984 to March 2004, 22 patients were admitted after being bitten by coral snakes. Twelve cases (ages 7 y–48 y, median 23 y; female, N=6; male, N=6) fulfilled the inclusion criterion: confirmed cases (snake brought for identification, N=4) and highly suspected cases (neurotoxic envenoming, N=8). Four patients were bitten on the hands (fingers, N=3), two on the feet (finger, N=1) and two on the ankles. Most patients were admitted less than 3 h after the bite (N=8), and two more than 6 h. Cases were classified as dry bite (N=1, caused by *M. lemniscatus*); mild (local manifestations without neurotoxic syndrome, N=2, caused by *M. frontalis* and *Micrurus spp.*); moderate (mild myasthenia, N=6) and severe (important myasthenia, N=3, one of them caused by *M. frontalis*). The main clinical features upon admission were: paresthesia (N=10), local pain (N=9), palpebral ptosis (N=8), fang marks (N=4), weakness (N=4), inability to stand (N=3), muscle fasciculation (N=2), slight local edema (N=2), diplopia (N=2), superficial breathing (N=2), vomiting (N=2), headache (N=2), blurred vision (N=1) and difficulty in swallowing (N=1). No patient developed respiratory failure. Total CK were measured in 4 cases, being mildly elevated in one (two times above the reference value). Antivenom (I. Butantan, SP-Brazil; 1 vial=10 ml of Fab'2) was employed in 11 cases (5–13 vials, median=10 vials), being observed early reactions in 4. Anticholinesterase (neostigmine, N=2 and edrophonium, N=1) were tested in the three severe cases, with good response in two. No deaths were observed. *Conclusions:* The prognosis was good. As previously reported, a therapeutic test with anticholinesterase may be useful in severe cases caused by *M. frontalis*. *Micurus spp.* venoms are extremely toxic in experimental models, producing progressive flaccid paralysis and rhabdomyolysis. However, these accidents are uncommon because of several reasons (these snakes are not aggressive, live mostly underground, and are proteroglyphous with short fangs and a small mouth). Therefore, little or no venom is injected after most bites. Since only suspected cases with evident neurotoxic features were included, we cannot rule out the possibility that the 10 excluded cases were bitten by ''false coral'' snakes (opisthoglyphous), or were dry bites (N=6) or mild accidents (N=4) caused by *Micrurus spp.*

121. Intoxication Following Minor Stabs from the Spines of a Porcupine Fish

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Background: It is well known that consumption of tetrodotoxin (TTX) containing fish can lead to a severe intoxication. Porcupine fish (e.g. *Diodon hystrix*) contain TTX, a non-protein neurotoxin that is also found in other families of the Tetraodontiformes, such as the puffer family. Specific symptoms mentioned include paresthesia, dizziness, headache, nausea, ataxia, paralysis, and hypotension. Intoxications via other routes of exposure than ingestion are rarely reported in the international literature. We present a case in which intoxication is the result of minor stabs from the spines of a porcupine fish. *Case Report:* A porcupine fish, kept at an aquarium of Burgers' Zoo in the Netherlands, died of a skin infection by a ciliate (*Cryptocaryon spec*.). The curator of the aquarium, co-author of this case report, performed autopsy on the fish to verify the cause of death. Unfortunately, while handling the dead fish the spines of the fish penetrated his latex gloves, which resulted in 3 to 4 minor punctures in his left middle finger. After 1.5 hour the patient experienced paresthesia and numbness in this finger. He was familiar with the toxicity of TTX and went to a nearby hospital. In the following hours the paresthesia spread from the finger to his arm, shoulder and back. Further he developed paresis of his left arm and dizziness. He had no respiratory insufficiency. The patient also noticed an increase of urine production during the first 48 hours. Laboratory investigations revealed normal values for hemoglobin, leukocytes, thrombocytes, potassium, creatinine, gamma-GT, ASAT, ALAT, LDH, CRP. Urea 5.8 mmol/L, glucose 5.2 mmol/L. Sodium was slightly increased 146 mmol/l. The calculated plasma osmolality, 303 mosmol/kg, was slightly increased. No urine analysis was available. Headache developed 7 hours after exposure and persisted for 3 days. No other clinical signs were observed. An expectative policy without specific treatment was followed. The patient fully recovered after three days. *Conclusion/Discussion:* This incident caused a very unusual intoxication. It can be speculated that TTX from the intestine and abdominal organs entered the body via the minor wounds during the autopsy. The death of the fish might have caused some autolysis leading to more availability of TTX and therefore more contamination of the wounds. On the other hand, Malpezzi et al. (1) discovered neurotoxins in the secrete of the skin of the *Diodon hystrix*, which might cause some neurotoxic effects. Although, the puffer fish is handled frequently, the above-described phenomenons have not been reported previously, as far as we know. Perhaps autolysis of the fish might also be involved here. The slightly increased diuresis might be caused by TTX. Tambyah et al. (2) suggested that TTX block the sodium channels of the neurons of the supraoptic nuclei in the hypothalamus inhibiting the release of vasopressin and causing central diabetes insipidus. This might explain the slightly increased osmolality and urine production. *References:* 1. Malpezzi EL, de Freitas JC, Rantin FT. Occurrence of toxins, other than paralysing type, in the skin of Tetraodontiformes fish. *Toxicon* 1997; 35:57–65. 2. Tambyah PA, Hui KP, Gopalakrishnakone P, Chin NK, Chan TB. Central-nervous-system effects of tetrodotoxin poisoning. *Lancet* 1994; 343:538–539.

122. The Bite of *Atheris squamiger*

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Objective: Reports of envenomations by *Atheris squamiger* are rare. Usually symptoms are mild, but there are reports of massive coagulation abnormalities which can lead to severe bleeding. Since clinical experience of this envenomation is very limited, there is insufficient evidence on the optimal treatment of envenomations by *Atheris squamiger*. *Case Report:* A healthy 35 year-old snake keeper was bitten on his right index finger by an adult *Atheris squamiger* while cleaning the terrarium. He developed massive local swelling of his right hand and was suffering from drowsiness and headache. The initial treatment was immobilisation of the limb, treatment of shock with crystalloids and application of H1/H2 blocking agents as well as corticosteroids. All laboratory findings were in normal range. The patient developed no systemic or local signs of coagulation abnormalities. 3 days after admission the patient could be discharged and could be managed in an ambulatory setting. The patient was suffering from local symptoms due to lymphadenopathy for several weeks before making a full recovery. *Conclusion:* Since there is no specific antivenom available, treatment of *Atheris squamiger* evenomations is based on therapy for shock, immobilisation, as well as clotting factor replacement therapy for treating coagulation abnormalities if necessary.

123. Acute Poisoning with Paradise Nuts (*Lecythis ollaria*): Case Report

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Objective: Selenium poisoning by natural products has been known for a long time, but observed rarely in Europe. We describe an acute non intentional selenium poisoning with delayed diagnosis caused by ''paradise nuts.'' *Case Report:* A 46 year old previously healthy woman developed headache, dizziness, nausea, restlessness, cramps, and weakness of unknown origin. Two weeks later she suffered from increasing hair loss. On week 3 she noticed greyish discoloration lines on all fingernails. With the exceptions of sonographic signs of a hepatic steatosis and rare supraventricular extrasystoles the clinical and laboratory investigation showed normal results. On week 6 the patient recognized that a woman working in the same office was suffering from similar symptoms along an equal time course. Both had ingested a handful of selenium-rich ''paradise nuts'' (*Lecythis ollaria*) when visiting an oil mill factory the day on which the early symptoms had appeared. No other visitors had tasted the nuts and nobody else had developed symptoms. A causative relationship was suspected: on week 8 the plasma level of selenium was determined to be 0.479 mg/L (normal range: 0.074—0.139 mg/L), one week later 0.300 mg/L, and on week 14 was 0.246 mg/L. After 12 months all symptoms had decreased, selenium in serum was 0.152 mg/L, selenium urine concentration 0.026 mg/L (0—0.031 mg/L), and selenium excretion in urine was 9,1 micrograms/24 h. *Discussion:* It has been known for some time that nuts of *Lecythis ollaria* accumulate substantial amounts of seleno-cystathionin when growing on selenium-rich grounds in South America (Kerdel-Vegas et al., 1965). Several selenium poisonings after ingestion of 7 or more of these nuts are documented in the literature (Kerdel-Vegas, 1966). The symptoms described before are identical with the symptoms of the two patients described here. An increasing market of selenium substitution products in Europe includes products of biological origin. Selenium poisonings caused by *Lecythis ollaria* or other selenium accumulation plants may increase. *Conclusion:* Ingestion of *Lecythis ollaria* nuts may cause selenium poisoning with reversible symptoms difficult to recognize. *References:* Kerdel-Vegas F, Wagner F, Russell PB, et al. Structure of the pharmacologically active factor in the seeds of *Lecythis ollaria*. *Nature* 1965; 205:1186–1187. Kerdel-Vegas F. The depilatory and cytotoxic action of ''Coco De Mono'' (*Lecythis ollaria*) and its relationship to chronic seleniosis. *Econ Bot* 1966; 20:187–195.

124. Lack of Coagulopathy from American Copperhead Envenomation, Regional Poison Center Experience

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Objective: Crotalidae envenomations have been shown to cause significant coagulopathy. Minimal literature exists describing the coagulopathic effects of envenomation specifically by the American Copperhead, *Agkistrodon contortrix*. A retrospective study was undertaken to investigate the effects of copperhead envenomation on the clotting parameters. *Methods:* A retrospective chart review was preformed on all Copperhead envenomations called to a regional poison center and treated at the center's host hospital. The charts were reviewed for results of prothrombin time (PT), partial thromboplastin time (PTT), international normalized ratio (INR), and platelet count. *Results:* A total of 18 charts collected from a 3 year time period (2001–2004) were reviewed. Laboratory data was reviewed for peak values of PT, PTT, and INR. The average PT was 11.01 seconds (SD 0.69) (normal value: 9.2–12.5 seconds) with a median of 11 seconds. The average of the INR was 1.05 (SD 0.89) (normal value of 0.9–1.2) with a median of 1.00. The average PTT was 28.31 seconds (SD 4.80) (normal value: 24.5–34.5 seconds) with a median of 28.90 seconds. The average platelet count was $284.28 \times 10^3/mm^3$ (SD 82.77) with a median of $261.00 \times 10^3/mm^3$. Only one patient had abnormal, results with a PT of 12.7 seconds, INR of 1.3 and PTT 38.1 seconds. *Conclusion:* Based on data reviewed, American Copperhead envenomation does not appear to have a significant effect on the human clotting parameters. This study is limited by its small sample size and should be repeated in a prospective fashion.

125. Some Epidemiological and Clinical Data from Bees and Wasps Stinging Patients Attended by Unicamp Poison Center (UPC), Brazil, 1994–2003

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Objectives: To present data from bees and wasps stinging patients attended by UPC 1994–2003 and some clinical data from cases of internment at the Emergency Infirmary (EI) of the University Hospital (UH). *Methods:* A retrospective review of data

TABLE 1
Multiple stings by bees patients interned in the EI of the UH

Year	Age/sex	Time in hospital	Number stings	ARF	Rhabdomyolysis	Hemolysis	Evolution	Others
1987	48F	36d	1,400	Y	Y	Y	Cure	Shock
1987	33M	8d	1,600	Y	Y	N	Cure	Shock
1995	67M	2d	400	N	N	N	Cure	–
1997	50F	3d	100	N	N	N	Cure	–
1998	30M	8d	68	Y	Y	N	Cure	–
1999	63M	3d	100	N	N	N	Cure	–
2000	83M	3h	200–300	Y	ND	ND	Death*	Shock
2002	56F	15d	400	Y	Y	N	Death	Shock

ARF=acute renal failure; ND=not done.
*Cardio-respiratory arrest (CRA) on admittance.

of bees and wasps accidents of UPC from Jan 1994 to Dec 2003. *Results and Cases:* From Jan. 1994 to Dec. 2003, the UPC attended 35,939 patients, from them 7,832 were accidents with venomous animals, and from these 522 with bees and 132 with wasps. Among the 522 patients attended by bees stings 4 died, 2 at the UH, and 1 before arriving at the UH and 1 in another hospital. Table 1 summarizes the main information on multiple stings by bees patients interned in the EI of the UH. The most severe cases interned in the EI of the UH were 4 patients: 1) A 48-year-old female attended in 1987, stung by about 1,400 bees, presented shock, rhabdomyolysis, myoglobinuria, hemolysis with hemoglobinuria, ARF that needed hemodialysis during 22 days, jaundice hepatitis, but survived and was sent home in good condition. 2) A 33-year-old man, attended in 1987, some week and town of the first one, stung by 1,600 bees, presented shock, rhabdomyolisis, ARF, but didn't need hemodialysis. 3) A 83-year-old man, attended in 2000, stung by about 200–300 bees, who had previously myocardial infarct and 3 cerebral vascular accidents, presented, on admittance, cardio-respiratory arrest (CRA) and died at ER; 4) A 56-year-old female attended in 2002, stung by 400 bees, whose husband died at the local of the accident. She presented rhabdomyolysis, developed ARF, submitted to hemodialysis, had infection and died after 15 days in hospital. *Comment:* Multiple bee stings may lead to death, especially before arriving at a hospital.

126. German Classification of Poisonous Plants

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Objectives: Systematic findings made by mankind over the centuries have resulted in the knowledge that a defined share of the plants is inedible or poisonous. We have started an assessment of the toxicity of plants to enable the Public Health Departments and Poison Control Centres (PCC) to provide, amongst other information, objective medical advice and substantiated recommendations for plants that would be safe if grown in close proximity to kindergartens, schools and public parks. The project was funded by the BMU (FKZ 700 67 001). *Method:* The 82 most common plants (except mushrooms) of the geographic region of central Europe were listed by their common German name, relating synonyms and the Latin name. Following the assessment of the toxicity of chemicals in analogy to the German Regulations on Dangerous Substances, we classified the plants into three categories, namely plants which could lead to (+) minor poisoning, (++) moderate poisoning and (+++) severe or deadly poisoning. The table of poisonous plants has been arranged in an alphabetical order and by growth size of the plants (tree, bush or grass-like). The final table of poisonous plants will have its counterpart in a list of 62 non-poisonous plants appropriate for being used in the close proximity of childrens' playgrounds, kindergartens, schools etc. *Results:* The German classification of poisonous plants contains useful information on 144 different plant species. 62 were to be considered as non-poisonous and 82 were rated as poisonous to a varying degree. In the category of the severe and deadly plants, there were 12 plant species including the most poisonous monkshood (*Aconitum napellus*), meadow saffron (*Colcicum*), castor-oil plant (*Ricinus*

communis), water hemlock (*Cicuta virosa*), cowbane (*Cicuta maculata*) and poison hemlock (*Conium maculatum*). It makes sense to clear all playgrounds, public parks, schools and gardens of these highly poisonous plants. Cases of ingestion of these plants have to be treated as emergencies. Parents of young children are advised to learn how to recognise these 12 highly toxic plants, if they live close to parks, gardens and the outdoor nature. They should contact a PCC, if they have the slightest suspicion of a contact of their children with such poisonous plants. Depending on the dose, ingestion of one or several of 30 plants having a moderate toxicity will normally lead only to minor to moderate manifestations. *Conclusions:* The German classification of poisonous plants is very helpful for the medical treatment and for recommendations on safe plants to be used in the environment of children. The results were published in the ''Bundesanzeiger'' (Federal Gazette) and in a widely distributed BfR-brochure entitled ''Poisonous Plants.''

127. Venous Thromboembolism Following *Trimeresurus mucrosquamatus* Snakebite

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Objective: Systemic thrombosis, mainly arterial thrombosis, has been noted among patients who developed disseminated intravascular coagulation following snakebites. Venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE), however, is an extremely rare complication following poisonous snakebites. We report two patients who developed VTE after they were bitten by *Trimeresurus mucrosquamatus*. *Case Report:* Case 1. A 71-year-old woman manifested marked swelling and tenderness of right leg after being bitten by *Trimeresurus mucrosquamatus*. She was admitted to a local hospital and received specific antivenin therapy. Although she did suffer from palpitation, dizziness, and chest discomfort during the hospitalization, she was discharged 8 days later. Unfortunately, she experienced frequent dyspnea and palpitation, and two episodes of syncope in the next couple of days, and was referred to our service. Upon arrival, hypoxemia was noted despite oxygen supplementation (PO_2 60.6 mm Hg with 3 L/min oxygen). Other laboratory data were unremarkable. A diagnosis of PE was suspected, and was supported by the finding of ventilation/perfusion mismatch. Study for DVT, however, was unyielding. She was treated with thrombolytic therapy and anticoagulants. Follow-up ventilation-perfusion scan 9 days later showed marked resolution of PE and she was discharged on day 21. The likely cause of her VTE was prolonged immobilization. Case 2. A 52-year-old man presented to a local hospital with swelling, tenderness, and ecchymosis of right hand and forearm 30 minutes after being bitten by *Trimeresurus mucrosquamatus*. Because his symptoms worsened despite antivenin therapy, he was referred to our service 4.5 hours after the exposure. Physical examination revealed the presence of marked swelling and tenderness of right arm without evidence of neurological involvement. Laboratory data were remarkable for mild leukocytosis and rhabomyolysis (CPK 1,151 U/L). Another dose of antivenin was administered and he was hospitalized. Because his right arm remained markedly swollen 3 days later, doppler scan was performed, which revealed the presence of thrombosis of right brachial vein. Thrombolytic therapy and anticoagulants were commenced and his condition improved, although his CPK level peaked at 19,290 U/L on that day. Follow-up doppler scan 1 week later was negative. The likely cause of his VTE was severe limb compression with venous stasis. *Conclusion:* Snakebite by *Trimeresurus mucrosquamatus*, which contains phospholipase A2 and fibrinogenase, normally causes mild bleeding tendency without the coexistence of disseminated intravascular coagulation. However, severe *Trimeresurus mucrosquamatus* bite may result in prolonged immobilization or limb compression, which increases the risk of VTE. High index of suspicion is needed for prompt diagnosis and treatment of patients who manifest possible symptomatology of VTE.

128. Anticholinergic Syndrome Following Plant or Chinese Herb Exposures: A Review of 118 Cases

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Objective: Many plants contain alkaloids that possess anticholinergic properties. Accidental or intentional use of parts or products (e.g. Chinese herbs) of these plants may cause severe anticholinergic manifestations, such as coma, seizure, hyperthermia, severe hypertension/tachyarrhythmia, or even death. Although cases with anticholinergic plant/herb exposure have been previously reported, there is currently limited information about the demographic and clinical characteristics of such exposures in Chinese or other Asian population. *Methods:* Retrospective analysis of all cases reported to the Taiwan Poison

Control Center during 1986–2002 who were exposed to plants or herbs that may produce anticholinergic effects. Their demographic and patient characteristics were summarized and tabulated. *Results:* During the study period, there were 1,615 patients with plant/herb exposure. Among them, there were 83 incidents (118 cases) that involved an anticholinergic plant/herb exposure. Most incidents (89.2%) were caused by an exposure to Datura species. Using patients with other plant/herb exposures as the comparison group, patients with anticholinergic plant/herb exposures were more likely to be associated with acute oral exposure, increased age, misuse of herbal medicine, severe clinical course, and antidotal therapy. Following the ingestion of anticholinergic plants or herbs, most patients manifested either partial or full-blown anticholinergic syndrome. Although severe toxicity (e.g. coma, seizure, or high fever) was recorded in 17 patients, none of the patients died. Physostigmine was given in 21 patients and showed a good response in all of them. *Conclusion:* Anticholinergic plant/herb exposure is one of the leading causes of plant/herb poisoning in Taiwan. Unlike the common use of anticholinergic plants as a hallucinogen in many western countries, most patients in this study were exposed to the toxic substances due to misuse of herbal medicines or ingestion of wild vegetables. Following toxic exposures, most patients developed various anticholinergic features, which were readily managed by prompt supportive treatment and appropriate use of physostigmine. Although none of the patients died, more education is apparently needed in preventing similar incidents and/or fatality in the future.

129. Severe Persistent Coagulopathy Ten Days After Snake Bite

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Background: We present a case of severe, persistent coagulopathy 10 days after rattlesnake envenomation. *Case Report:* A 48 year old white male presented 3 hours after having been bitten by a Timber rattlesnake (*Crotalus horridus*). Puncture wounds were located on the right small finger and swelling extended to the wrist. Systolic blood pressure was 80–90 mm Hg and the GCS was 7–8. He was intubated and administered intravenous fluids, epinephrine and norepinephrine. The arterial blood gas revealed a pH 7.06, pCO_2 34, pO_2 309 with a base deficit of −18.9. There was no anion gap. His blood ethanol level was >300 mg/dL. The coagulation studies remained unmeasurable until after 16 units of fresh frozen plasma (FFP) and 10 packs of cryoprecipitate (cryo) were administered along with four vials of Crotalidae Polyvalent Immune Fab. Prothrombin time (PT) was 13.3 s, INR 1.4, and PTT 31 s at 12 hours post exposure. Serum creatinine was 1.5 (mg/dL) and platelet count was 214 K/UL. He was discharged home but presented 4 days post exposure with recurrent bleeding. Fibrinogen and fibrin split products at the time were unmeasurable; D-dimer was 1.55 mcg/ml (normal: 0.00–0.49). Over the next 6 days, multiple doses of vitamin K, 18 more units of FFP and 20 more packs of cryo were administered, with persistence of the coagulopathy. Six vials of Crotalidae Polyvalent Immune Fab were administered on day 10, after consultation with a Poison Center and the coagulopathy resolved. PT was 12.6 s and INR 1.2. *Conclusion:* This case describes prolonged coagulopathy after rattlesnake bite and emphasizes the importance of appropriate antivenin therapy, even after 10 days from the event. Crotalidae Polyvalent Immune Fab effectively reverted the coagulopathy induced by a rattlesnake bite.

130. Outcome Following Repeated Use of Wyeth Antivenin

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Background: Use of Wyeth-Ayerst's Crotalidae Polyvalent Antivenin is associated with life-threatening allergic reactions and serum sickness. This report describes seven separate administrations of antivenin to a single patient following repeated rattlesnake envenomations. *Case Report:* Over 18 years, a 33 year-old man, owner of several species of North American Crotalinae and routine participant of rattlesnake ''sacking,'' reported 11 bites with seven documented envenomations: *C. horridus horridus* (one), *C. adamateus* (two) and *C. atrox* (four). He was treated with antivenin seven times because of severe pain and progressive edema. Only after the seventh envenomation did the patient experience subjective 'throat tightening' during rapid administration of antivenin, despite a negative skin test. The symptoms resolved immediately after subcutaneous epinephrine and oral diphenhydramine. There is no record of other adverse reactions to repeated envenomation or antivenin use. The patient denied experiencing serum sickness or having a history of immune deficiency. HIV testing was refused. One prior hospital course was complicated by vascular compromise and infection at the bite site (hand), dermotomy, debridement and eventual amputation of two digits. *Conclusion:* We report the experience of a single patient with seven, separate treatments of

Wyeth-Ayerst's Crotalidae Polyvalent Antivenin after Crotalinae envenomations. Extrapolation to other patients and expected outcome is limited.

131. Accidental Colchicine Poisoning Due to Confusion of Wild Garlic with *Colchicum autumnale*: A Case Series

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Objectives: Leaves of *Allium ursium* have become more popular in cuisine and are prepared as salad, soup or used as spice. Confusion with *Colchicum autumnale* while collecting wild garlic is result of similarity of the leaves. Both plants grow sometimes in direct neighbourhood. Colchicine poisoning due to confusion with wild garlic (*A. ursium*) is frequently reported but until now a case series is missing. *Case Series:* We retrospectively analysed cases matching the following criteria: Poisoning due to confusion with wild garlic, sufficient follow up, reported to the poisons information centres GIZ-Munich (1/1994–4/2004) and VIZ-Freiburg (1/2000–4/2004). *Results:* 32 patients (age: 27–90 years, median 57) were included in this study. Sex ratio was: 19 female, 13 male. C. autumnale was identified botanically (26) or by urine detection of colchicine (6). Supposed leaves of wild garlic were ingested as salad (16), pesto sauce (4) or after cooking as soup (10) or vegetables (2). Severity of intoxication (poisons severity grade) was minor in 17, moderate in 6, severe in 3 and lethal in 6 cases. Patients developed vomiting and/or diarrhea 2–24 h (median 10 h) after ingestion. All patients developing symptoms after >9 hours showed a minor course. In 5 cases latency was unknown. If the leaves were boiled before eating (12/32) severity of poisoning was moderate, severe or lethal in 9 of 12 cases (75%), while ingestion of non-heated leaves caused in 6 of 20 cases (43%) a moderate, severe or lethal poisoning. Severity of poisoning was in the subgroup of elderly (66–90 ys, median 72 ys): minor (1); moderate (2), severe (3), lethal (5) and in the group of adults (27–65 ys; median 54 ys) minor (16), moderate (3), lethal (1). *Conclusions:* Decreasing sense of smell may be a reason why elderly people failed to notice the absence of the characteristic garlic odour while collecting the assumed *A. ursium*. Plasma half-life of colchicine in elderly is lengthened (30–34 h in contrast to 4.4 h) (1). According to this the elderly patients in this study were intoxicated more severely than younger ones. Preparation of C. autumnale leaves seems to influence severity of poisoning—possibly boiling increases availability of colchicine. *Reference:* 1. Rochdi M, Sabouraud A, Girre C, et al. Pharmacokinetics and absolute bioavailability of colchicine after i.v. and oral administration in healthy human volunteers and elderly subjects. *Eur J Clin Pharmacol* 1994; 46:351–354.

132. Generalized, Tonic-Clonic Seizure Associated with a Tiagabine Overdose in a Patient with No Prior Seizure History

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Objective: Tiagabine is used as adjunctive therapy for the treatment of patients with refractory partial seizures. Its anticonvulsant effect is due to its ability to inhibit the reuptake of gamma-aminobutyric acid. Several case series and reports describe nonconvulsive status epilepticus (NCSE) with tiagabine therapy and following overdose in patients with a seizure history. Only 2 case reports describe the development of NCSE following the use and overdose of tiagabine in patients without a seizure history. We report a case of a generalized tonic-clonic seizure, associated with a tiagabine overdose in a patient without a prior seizure history. *Case Report:* A 28 year-old woman with no prior medical history became unresponsive within 30 minutes after ingesting her boyfriend's medications, which may have included up to 50 tablets of tiagabine (2 mg/tablet), 15 tablets of propranolol (20 mg/tablet), and 3 tablets of sildenafil (amount/tablet unknown). On presentation to the emergency department, she was lethargic with an oral temperature of 37.4 degrees C, heart rate of 61/min, respiratory rate of 16/min, blood pressure of 108/63 mm Hg, and an oxygen saturation of 96% on room air. Her physical examination was otherwise unremarkable. Shortly after her arrival, the patient had a 5 minute generalized tonic-clonic seizure, which resolved with the administration of 2 mg of lorazepam. One hour later, she was still lethargic and had intermittent myoclonic jerking, which was not controlled with a total dose of 12 mg of lorazepam. She was intubated for airway protection and sedated with a propofol infusion. Orogastric lavage yielded pill fragments and the patient was given a dose of activated charcoal. Despite sedation with propofol, she had persistent

myoclonic jerking for several hours. An acetaminophen level was negative, and electrolytes and electrocardiogram were normal. About 20 hours post-ingestion, the patient was extubated and regained a normal mental status. Serum tiagabine level was 900 ng/mL. The upper therapeutic limit is 400 ng/mL. Propranolol was undetectable. *Conclusion:* This case represents the first report of a generalized, tonic-clonic seizure associated with a tiagabine overdose. It is also remarkable for the fact that the seizure occurred in a patient without a prior seizure history. This may have implications for triage of patients with unintentional ingestions of tiagabine.

133. Chronic Antiepileptic Drugs Poisoning in the Emergency Department

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Introduction: Many antiepileptic drugs (AED) have a narrow therapeutic margin, leading to frequent overdoses that may be prevented by monitoring of plasma concentrations. We analyze poisonings generated by chronic AED treatment, define their clinical characteristics and severity. *Methods:* The epidemiological, clinical and laboratory data of consultations in the Emergency Department for poisonings due to chronic treatment with AED were reviewed. *Results:* During a period of 36 months (2001–2003), 32 cases were detected: 18 due to phenytoin, 10 due to carbamazepine and 4 due to valproic acid. In 12 cases, there had been a recent change in the dosage, in 6 there was a concomitant disease or a pharmacological interaction and in 14 no precipitating cause was detected. The reasons for consultation were instability, altered gait, confusion and deterioration of the general health status. In the physical examination the most marked signs were nystagmus, dysmetria and reduced consciousness. Analytical tests showed hyponatremia in 5 patients, 4 of whom were receiving carbamazepine. Average plasma concentrations were 40.7 mcg/mL for phenytoin, 20 mcg/mL for carbamazeprine and 109.5 mcg/mL for valproic acid. Only five patients needed hospital admission and no patient died. *Conclusions:* Poisoning due to chronic AED treatment manifests in the form of non-specific neurological manifestations and requires a detailed history to establish the diagnosis and the triggering cause. *References:* Armijo JA, Valiente R, Herranz JL. Relation between plasma levels of valproic acid alone and its efficacy and toxicity in pediatric under chronic treatment. *Arch Farmacol Toxicol* 1981; 7:49–56. Collaborative Group for Epidemiology of Epilepsy. Adverse reactions to antiepileptic drugs: a follow-up study of patients with chronic antiepileptic drug treatment. *Epilepsia* 1988; 29:787–793. Howards CE, Roberts RS, Ely DS, Moye RA. Use of multiple-dose activated charcoal in pheytoin toxicity. *Ann Pharmacother* 1994; 28:201–203.

134. Serotonergic Excess and Discontinuation Syndrome in a Child

Gracia RG (1), Velez LV (2), Feng SY (3). 1. *North Texas Poison Center;* 2. *University of Texas Southwestern Medical Center; and* 3. *Children's Medical Center, Dallas, Texas, USA.*

Background: We describe a therapeutic error resulting in serotonergic symptoms followed by symptoms of withdrawal upon discontinuation. *Case Report:* An 18-month old white male presented with increased irritability, dysuria, ''crying and grabbing of private areas,'' diaphoresis, flatulence, 2–6 loose stools/day for 2 weeks, decreased oral intake with a 3 lb. weight loss, and decreased activity. It was discovered that his omeprazole (Prilosec) had mistakenly been filled with fluoxetine (Prozac) 10 mg BID for 6 weeks. Vital signs were blood pressure 101/51 mm Hg, heart rate 126 beats/minute, respiratory rate 24 breaths/minute, and temperature 36.6°C. No laboratory abnormalities were detected, and a comprehensive urine toxicology screen was only was positive for acetaminophen. Fluoxetine was immediately discontinued. He was observed for 24 hours with resolution of symptoms. Two days after discharge, the patient presented again with a fever of 102.9°F, decreased oral intake with an additional weight loss of 2 lbs, increased drowsiness and emotional lability. Vital signs were blood pressure 119/46 mmHg, heart rate 120 beats/minute, and respiratory rate 26 breaths/minute. A sepsis workup including urine, blood and spinal fluid cultures, and West Nile virus titers were negative. A fluoxetine level was 372 ng/ml (91–302 ng/ml) and a norfluoxetine level was 264 mg/ml (72–258 ng/ml). Over the next 24 hours, his activity and appetite increased and the fever resolved; he was discharged home. *Conclusions:* This case demonstrates serotonergic excess due to a dispensing error. It also describes the serotonin discontinuation syndrome in a pediatric patient following a brief but intense exposure to fluoxetine.

135. Serum Glutamine Level as Marker of Valproate-Induced Hyperammonemic Encephalopathy

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Background: The pathogenesis of valproate-induced hyperammonemic encephalopathy (VHE) is unclear. Measurement of serum ammonia is helpful in the diagnosis of VHE. Hyperammonemia may produce encephalopathy via inhibition of glutamate uptake by astrocytes, and increased glutamine production. It is thought that glutamine may be a more sensitive diagnostic test for VHE. We report a case of VHE with elevated ammonia, but normal glutamine levels. *Case Report:* A 21 year old male was admitted with valproic acid (VPA) and paroxetine overdose. He had by history taken 7.5–10 grams of VPA, and 200–400 mg of paroxetine tablets. On physical examination he was noted to be somnolent and confused. He was afebrile. His vitals were HR 140/min, BP 139/84; RR 18/min. Exam was non-focal, and abnormal only for mild somnolence. His initial VPA level was reported at 196 μg/mL (50–150). His liver function tests were normal. The next day the patient was noted to be increasingly somnolent. The VPA rose to 309 μg/mL. The ammonia was 317 μmol/L and glutamine was reported at 52 μmol/dL (normal<101). The patient was given l-carnitine with improvement in mental status changes. The VPA levels decreased to 137 μg/mL. The ammonia fell to 55 μmol/L, and glutamine was 63 μmol/dL. The patient did well and was transferred to psychiatry. *Conclusion:* Glutamine levels are thought to be useful adjunctive laboratory tests for the diagnosis of VHE. In our patient with VHE, the glutamine levels were normal and no correlation was found between hyperammonemia, mental status change and glutamine levels.

136. Acute Pediatric Donepezil Overdose Presenting as a Cholinergic Toxidrome

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Introduction: Donepezil (Aricept) is a commonly prescribed medication for the treatment of Alzheimer's disease. It is a reversible, noncompetitive acetylcholinesterase inhibitor. We present a case of a 2-year-old girl with an acute ingestion of donepezil presenting with cholinergic findings. *Case Report:* A previously healthy 21/2-year-old 14 kg female was brought to the emergency department (ED) shortly after a witnessed ingestion of a 10 mg tablet of donepezil. One-hour post ingestion the mother noticed the child becoming sleepy and complained of a headache followed by an episode of urinary incontinence. In the ED the child had a pulse of 86 bpm, blood pressure 131/76 mm Hg, temperature 36.5°C rectally, and a respiratory rate of 16/min. The child was somnolent and appeared confused. Her pupils were 2–3 mm. She had nasal discharge and was drooling. Her extremities demonstrated repeated episodes of fasciculations and a coarse, non-intentional tremor. The patient was placed on a cardiac monitor but never developed any significant bradycardia. Her initial potassium was 2.8 mEq/L. The physician elected not to treat her with atropine. Her potassium was supplemented. She was admitted for observation and had complete resolution of her symptoms over the next 12 hours. She was discharged home the following day with no further adverse events. *Discussion:* Donepezil is a piperidine based reversible and noncompetitive inhibitor of acetylcholinesterase (AChE). The medication was introduced in 1997 as a second-generation centrally acting AChE inhibitor for the treatment of Alzheimer's disease. It is structurally dissimilar from other established cholinesterase inhibitors such as carbamates, physostigmine, and tacrine. Donepezil has a high bioavailabililty without active metabolites. Donepezil has demonstrated activity in the cortex, hippocampus, striatum, and hypothalamus and follows a dose dependent response. Postsynaptic neurons appear to be more sensitive than presynaptic cholinergic fibers and studies have demonstrated some donepezil peripheral effect. In general, the lack of specificity for peripheral AChE in centrally acting AChE inhibitors is poorly understood, however, donepezil at or above 2.5 mg/kg consistently caused fasciculations. In addition, hypokalemia has not been shown to be an adverse effect of donepezil therapy. Treatment of donepezil toxicity is presumably the same as other AChE inhibitors. It is not clear whether an oxime compound such as pralidoxime is beneficial in the treatment of acute donepezil toxicity. *Conclusion:* Donepezil overdose may result in cholinergic findings. Central AChE inhibition appears to predominate but peripheral effects do occur.

137. S100B Protein in Benzodiazepine Poisoning

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Objective: Benzodiazepines are relatively safe and deaths caused by benzodiazepine ingestion alone are extremely rare. However, profound central nervous depression with significant respiratory depression and hypotension after benzodiazepine overdose might result in cerebral hypoxia and necrosis. The aim of the study was to assess the possible role of S100B, the structural protein of astroglia, as a biochemical marker of brain injury in benzodiazepine poisoning. *Methods:* The prospective study included 23 consecutive patients poisoned with benzodiazepines who were admitted at the Emergency Department (ED) in University Medical Center Ljubljana. Patients were enrolled if they had a documented exposure to benzodiazepine only. The physical and neurological examinations were carried out on the scene and on arrival at the ED. A conciseness level was assessed by alert/verbal/painful/unresponsive responsiveness scale. Blood samples for S100B determination were drawn immediately after arrival at the ED. S100B concentrations were measured with a commercial immunoassay. The control group included 10 healthy volunteers. Data are presented as mean and numerical variables were compared using the Mann-Whiteney U test. A p value of less than 0.05 was considered to be significant. *Results:* S100B levels of 23 benzodiazepine poisoned patients were significantly higher compared to S100B levels of the control group (0.36 microg/l versus 0.07 microg/l, $p<0.05$). 9 (39%) benzodiazepine poisoned patients were unconcious and unresponsive to painful stimulation at the scene. Their S100B levels were significantly higher compared to S100B levels of the benzodiazepine poisoned patients that were unconscious, but responsive on painful or verbal stimulus (0.73 microg/l versus 0.13 microg/l, $p<0.05$). All patients survived. *Conclusion:* Benzodiazepine poisoning is associated with elevated S100B levels. The unconcious patients unresponsive to painful stimulation after benzodiazepine poisoning had significantly higher S100B levels compared to the patients responsive to stimulation. S100B could be useful biochemical marker of benzodiazepine poisoning. Its clinical value should be further evaluated. *Reference:* Kelly CA, Upex A, Bateman DN. Comparison of consciousness level assessment in the poisoned patient using the alert/verbal/painful/unresponsive scale and the Glasgow Coma Scale. *Ann Emerg Med* 2004; 44:108–113.

138. Topiramate Overdose and Hyperchloremic Metabolic Acidosis

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Background: Topiramate (TPM) is a novel antiepileptic medication with multiple mechanisms of action, including inhibition of carbonic anhydrase. Metabolic acidosis is well documented but an infrequent adverse event. We report a patient with topiramate overdose and hyperchloremic metabolic acidosis. *Case Report:* A 15 year old female overdosed on approximately 3.5 gram of sertraline, 2.0 gram of oxcarbazepine, and 3.0 gram of topiramte. She was intubated because of mental status change and poor respiratory effort. The laboratory indicated normal electrolytes at presentation; however she developed a non-anion gap acidosis within 6 hours of the overdose. Her electrolytes were Na 143, K 3.8, Cl 113, CO_2 16, BUN<0.2, and Cr 0.6. Her ABG was pH 7.25, pCO_2 38, PO_2 72, HCO_3 16, Base excess-10. The patient was started on a bicarbonate infusion, and the acidosis resolved spontaneously over a period of 3 days. The comprehensive drug screen showed benzodiazepines, topiramte, sertraline and metabolites, TCA and metabolites, and carbamazepine. The patient was quickly extubated and did well. *Conclusion:* Topiramate overdose can result in non-anion gap acidosis in overdose. This may be due to inhibition of renal cortical carbonic anhydrase at the proximal renal tubule, resulting in impaired proximal bicarbonate reabsorption. The acidosis resolved over 3 days in our patient, and the treatment was essentially supportive.

139. Simple Assessment of Conscious Level in the Poisoned Patient

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Objectives: A number of methods are available to assess conscious level. Assessment tools such as AVPU have been shown to provide a rapid method of assessing conscious levels in toxicology patients and appear to be simpler to use than the Glasgow Coma Score (GCS). AVPU rates patients as being alert (A), responsive to voice (V), responsive to pain (P) or unresponsive (U). An alternative tool, ACDU, was suggested to distinguish groups in the mid range of GCS better than AVPU. ACDU scores patients as alert (A), confused (C), drowsy (D) and unresponsive (U). These four point scales may not provide adequate dispersion over the range of consciousness therefore a new five point scale, ACDPU, was introduced in this study. ACDPU

scores patients as alert (A), confused (C), drowsy (D), responsive to pain (P) or unresponsive (U). Our aim was to compare AVPU, ACDU and ACDPU with GCS in poisoned patients to identify which of these simple tools would be most useful as a method of assessing conscious level. *Methods:* AVPU, ACDU, ACDPU and GCS were recorded prospectively by one individual in a random selection of patients admitted to the toxicology unit of a university teaching hospital with accidental or deliberate poisoning. Each group of four conscious level assessments were recorded separately by one individual. AVPU, ACDU and ACDPU were performed in a random order and GCS was performed last in all cases. Box and whisker plots were used to determine correspondence between each assessment tool and GCS. *Results:* Conscious level was assessed in 140 toxicology patients. AVPU scores A,V, P and U were found to correspond to median GCS scores of 15,14, 6 and 3 respectively. ACDU scores A, C, D and U corresponded to median GCS scores of 15, 14, 13 and 4 and ACDPU scores A, C, D, P and U to median GCS scores of 15, 14,13, 6 and 3 respectively. AVPU and ACDPU provided the best dispersion of ranges of conscious level. Although each component of all three scales studied provided a statistically distinct range of GCS scores, the narrowest interquartile ranges for component points were described using AVPU. *Conclusion:* AVPU, ACDU and ACDPU correspond to similar distinct ranges of GCS in toxicology patients. The four point scale, AVPU appears to distinguish variations in conscious level in a manner that was more useful than the four point scale, ACDU, and as effectively as the 5 point ACDPU scale. Differentiation of confusion and drowsiness did not appear helpful in this small pilot.

140. Tiagabine Facilitated Serotonin Syndrome in a Child

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Background: Tiagabine is a P450 3A4 metabolized GABA reuptake inhibitor used to treat seizures. Escitalopram (S-isomer of citalopram) has been praised for its safety due to its selectivity for 5-HT receptors as well as its metabolism through multiple hepatic enzymes in the P450 system (CYP 2C19, 2D6 and 3A4), theoretically reducing the likelihood of drug interactions. Quetiapine, an atypical antipsychotic with 5-HT_{A1} and dopamine antagonistic effects is also metabolized by the P450 3A4 system. Escitalopram and quetiapine have been implicated in serotonin syndrome (SS) while tiagabine has no reported serotoninergic effects. *Case Report:* A 9 year old male with bipolar disorder treated with escitalopram, tiagabine and quetiapine presented to the emergency department (ED) after his tiagabine regimen was increased from 4 mg twice a day to 8 mg in the morning and 4 mg at night. Several hours following his medication increase, he became hyperactive culminating in severe agitation. On arrival the patient was combative, afebrile, tachycardic and hypertensive. Examination revealed 7 mm reactive pupils, facial flushing, and dry skin. He had no focal deficits and normal muscle tone but marked lower extremity hyperreflexia. EKG and serum electrolytes were unremarkable. He failed to improve with 0.02 mg/kg IV physostigmine; his agitation was managed with lorazepam. He was also treated with cyproheptadine with resolution of symptoms 19 hours after presentation. *Conclusion:* In this patient, the increase dosage of tiagabine precipitated SS most likely via competition of three medications for the same metabolic pathway.

141. Valproic Acid Induced Pseudohypercreatininemia

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Background: Several drugs can induce a rise in plasma creatinine concentration, interacting with different aspects of creatinine physiology without reduction in renal function. We report a case of valproic acid (VPA) induced hypercreatininemia with normal renal function. *Case Report:* A 42 year-old male overdosed on 45 grams of VPA following an argument with his wife. He presented to the emergency department and was found to be lethargic, and then became progressively stuporous. He was intubated for airway protection. His exam was otherwise unremarkable. The initial valproic acid level was elevated to 1000 μg/mL and peaked at 1157 μg/ml. The patient also developed hyperammonemia and was treated with l-carnitine. His initial creatinine level was 1.7 mg/dL (0.4–1.2) with urea nitrogen of 18 mg/dL (5–20). The total CPK was 357 IU/L. The creatinine remained elevated for 48 hours and fell to 1.2 mg/dL when the valproic acid level reached 68 μg/mL. The patient maintained a good urine output throughout with normal urea nitrogen. The patient did well and was transferred to psychiatry. *Conclusion:* VPA therapy is well known to produce proximal renal tubular dysfunction. VPA may cause competitive inhibition of creatinine

secretion in the proximal tubules. This may result in spuriously elevated creatinine levels without any impairment of renal function.

142. Cinnarizine-Induced Seizures in a Pediatric Patient

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Background: Cinnarizine is a piperazine derivative with antihistaminic, sedative and calcium channel blocking activities. Although widely used for vestibular disturbances, data about poisoning is very limited. *Case Report:* A previously healthy 30 month old child weighing 13 kg with no known history of seizures was admitted to the ED in a state of unconsciousness. According to her parents she had been playing 4.5 hours previously with a box of cinnarizine; nine 25 mg tablets were missing. Her parents denied all other medications at home except for acetaminophen. On examination she reacted to deep pain only, GCS 8, had normal vital signs, spontaneous respiration with normal O_2 saturation and normal ECG. She was treated with gastric lavage and IV fluids. Soon after admission she had three short episodes of general convulsions that were controlled with 2 mg diazepam IV. She was admitted to the PICU and gradually regained consciousness. No Parkinsonism developed. In the following day her neurological and general physical examinations were normal. The laboratory results showed transient hypokalemia (2.8 mEq/L) and microcytic anemia (Hb10.5 g/dL). Acetaminophen level was below the limit of detection. The patient was discharged in good health 24 hours after admission. She remained normal on follow up with both her parents and pediatrician. *Conclusion:* A case of CNS depression and seizures following cinnarizine overdose (15–30 fold the therapeutic dose) in a pediatric patient is reported. Although cinnarizine blood level was not determined, the reliable history, compliant family and absence of other drugs in the home except for acetaminophen as well as the similarity of clinical effects to those of other antihistamines, all support the diagnosis of cinnarizine induced stupor and seizures. The underlying mechanism for cinnarizine induced seizures is unclear. It is hypothesized that antagonism at muscarinic cholinergic, serotonin and alpha adrenergic receptors and possibly exaggerated calcium channel blocking activity could have contributed to this phenomenon. Although uncommon, cinnarizine overdose patients need to be observed for potential neurological complications.

143. Overdose with the New Atypic Neuroleptic Drug Aripiprazole (Abilify®) with Little Symptoms

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Case Report: A 57 y female took 84 tablets of 15 mg aripiprazole in a suicidal attempt. She vomited spontaneously soon after the ingestion and was admitted to our hospital 21/2 h later. Her medication for paranoid schizophrenia has been aripiprazole 15 mg daily for 5 weeks. She has been suffering from myasthenia gravis for about six years, which had been treated with thymectomy 5 years ago. Her medication has been pyridostigmine 60-10-60 mg p.o. and azathioprin 50 mg p.o. daily since. On arrival she reported drowsiness and nausea. Except for muscle weakness in the upper extremities dropping eyelids and a tachypnea 24/min her examination gave no pathologic findings. Her BP was 128/73 mm Hg, HR 71/min, pulsoxymetric SaO_2 95% while breathing ambient air. Her ECG was normal, so was routine laboratory testing. Her peak flow was 340 l/min (normal: >450 l/min). She received 20 g activated charcoal p.o. and pyridostigmine 0.17 mg/h i.v. Observation in the ICU was uneventful. She felt completely recovered and received her regular antimyasthenic medication. Her peak flow was 330 l/min. On the 3rd day she was transferred to a psychiatric ward. *Discussion:* Aripiprazole is an atypic neuroleptic drug with partial antagonistic dopamine D2 and antagonistic serotonine 5HT2A effects. Serum levels of aripiprazole in our patient were 3.09 mg/l 21/2 h after ingestion, 1.78 mg/dl after 6 1/2 h and 0.93 mg/l after 23 h (half life 15 h (r^2=0.92 1st order kinetic). Therapeutic serum concentrations are 0.3–0.5 mg/l (1). Plasma half-life with therapeutic doses is 75 h (2). This is, to our knowledge, the first report of a significant aripiperazole overdose, exhibiting no severe symptoms. However, we found in our patient a shorter half-live of aripiprazole than reported in the literature. Aripiprazole is metabolized by CYP2D6 and CYP3A4 (3). Other medication of our patient could not have influenced these enzymes. The short half-life of aripiprazole in our patient may have been caused by an individual fast metabolism, an altered kinetic after overdose, or an effect of the activated charcoal, interrupting enteral reabsorption. *References:* 1. Citrome L, Josianssen R, Bark N, et al. Pharmacokinetics of Aripiprazole and concomitant mood stabilizers [abstract]. *Int J Neuropsychopharmacol* 2002; 5 (Suppl 1):187. 2. Mallikaarjun S, Salazar DE, Bramer SL. Pharmacokinetics, tolerability and safety of aripiprazole following single and multiple oral dose administration.

Eur Neuropsychopharmacol 2000; 10 (Suppl 3):306. 3. Keck PE Jr, Mc Elroy SL. Aripirarole a partial dopamine D2 agonist antipsychotic. *Expert Opin Investig Drugs* 2003; 12(4):655–662.

144. Is the Measurement of Serotonin Level Useful in Selective Serotonin Reuptake Inhibitor Antidepressant Overdoses?

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Objectives: Incidence of the selective serotonin reuptake inhibitor (SSRI) antidepressant acute overdoses is increasing due to large prescriptions. However, clinical presentation of poisoned patients is not specific, even when serotoninergic syndrome is present (1). The objectives of our study was to describe the most severe SSRI poisonings admitted in ICU and to analyze the variations of their serotonin levels on admission. *Methods:* Prospective study including all the patients admitted in 2002–2004 for a SSRI poisoning (defined by a toxic SSRI plasma level measured using HPLC—REMEDI), excluding any other serotoninergic toxicant. Serotonin was measured on admission in blood, plasma and platelets using HPLC—fluorimetric detection. The ethics committee of the Société de Réanimation en Langue Française approved the study. Results are presented as median [10–90% percentiles]. *Results:* Twenty-two patients (8M/14F, 40 years [24–50], SAPS II 34 [15–56]) were included. Ingested SSRIs included venlafaxine (9/22), paroxetine (5/22), citalopram (4/22), fluoxetine (2/22) and sertraline (1/22). Overdoses were multidrug poisonings (86%). The most frequent failure presented on admission was coma (Glasgow Coma Score <8: 50%). Symptoms related to the serotoninergic syndrome were sometimes present: confusion (18%), hallucinations (5%), agitation (5%), seizures (5%), motor incoordination (5%), mydriase (27%), hypertonia (23%), exacerbated osteotendinous reflexes (45%) or pyramidal syndrome (18%). Significant prolongation of PR, QRS or QTc was found (10%) but only 1 case of cardiogenic shock observed. Treatment included mechanical ventilation (14/22), fluid replacement (5/22), sodium bicarbonate (3/22) and catecholamines (3/22). No patient died. SSRI plasma concentration was 5,0 [1,3–16,9] times more elevated than the toxic cut-off. We found a significant increase of the plasma serotonin (15,8 nmol/l [9,2–33,6], N: 2,0–15,0), a significant decrease of the platelet serotonin (0,170 aM/plaquette [0,046–0,609], N: 0,50–5) and a normal blood serotonin level (94 nmol/l [39–431], N: 100–900), in comparison to non-SSRI poisoned patients. *Conclusions:* The serotoninergic syndrome clinically defined by Sternbach (1) is difficult to recognize. Our results show the interest of plasma and platelet serotonin level measurement in SSRI poisonings. Decrease of platelet serotonin level may represent a marker of long-term treatment, while increase of plasma serotonin level may result from the huge SSRI acute ingestion. *Reference:* 1. Sternbach H. *Am J Psychiatry* 1991; 48:705–713.

145. Citalopram Poisoning and Fatality

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Objective: Reports on poisoning with citalopram suggest that it may be more toxic than other selective serotonin reuptake inhibitors. We analysed our cases to give more information about dose-toxicity relationship. *Case Series:* From July 1997 to October 2004 our PIC recorded 93 cases (7 children, 86 adults) with single citalopram ingestion. Suicide attempts represent the main proportion of all cases (68%), the others were accidental overdoses (11%) or the cause was unknown. The age of the patients ranged from 2 to 79 years (median 34 years), 71% were female. Ingested dose ranged from 1.5 to 600 fold DDD (20 mg/day). The risk was assessed to be moderate in 11% and high in 6.5% of the patients. The clinical feature were predominantly characterised by CNS depression (70%) and gastrointestinal disturbances. Seizures were observed in 15% of the patients (above 30 fold DDD). Furthermore, patients presented cardiovascular symptoms (23%) especially tachycardia (above 15 fold DDD). In 3 cases arrhythmias were reported (above 30 fold DDD). *Case 1:* A 52-year-old female ingested 2000 mg (approx. 28 mg/kg) probably 12 hours before admission. She suffered a seizure at home. Blood alcohol concentration was 1.7 gram/L. Blood pressure was 140/80 mm Hg, heart rate 120 beats/min. Despite the late admission activated charcoal and sodium sulphate were given. QTc was normal (383 ms). No further seizure or cardiac dysrhythmias occurred. The patient was transferred the next day to a psychiatric department. *Case 2:* A 22-year-old female ingested 4000 mg (approx. 57 mg/kg). A persistent common atrioventricular canal had been treated surgically in the previous year. The admission was very late, probably 6 to 9 hours after ingestion. She was somnolent with progression to coma. Initial blood pressure was 100/60 mm Hg and heart rate 100 beats/min. Unfortunately, an ECG was not

passed on the poison centre. Even though patient was admitted late, activated charcoal was administered. Already preclinically existing tonic-clonic seizures recurred at the intensive care unit and asystole occurred. Initial cardiac resuscitation was successful. The patient was intubated and artifically ventilated. A temporary pacemaker was inserted as a bradycardic escape rhythm appeared. The patient died under renewed unsuccessful resuscitation. *Conclusion:* Regarding the central as well as cardiac toxicity of citalopram we confirm case reports from the literature (1,2) that doses over 2 grams provoke severe symptoms, whereas about 4 grams may be a lethal dose. *References:* 1. Öström M, Eriksson A, Thorson J, Spigset O. Fatal overdose with citalopram. *Lancet* 1996; 348:339–340. 2. Personne M, Persson H, Sjöberg E. Citalopram toxicity. *Lancet* 1997; 350:518–519.

146. Manganese-Induced Parkinson's Syndrome

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Objective: We describe a potential cluster of 10 patients with occupational exposures to manganese who developed a neurologic syndrome that resembles Parkinson's Disease. All of these patients are currently retired and had varying job descriptions. *Case Report:* A 75-year-old who worked in a shipyard for forty years had three job titles during his employment. These were (1) Carpenter in the model shop (2) scheduler in the planning department, and (3) Purchasing Agent. The latter two jobs involved plant visits and time on the shop floor. He spent 3–15 hours a month observing welding operations without personal protective equipment. The patient presented with a 3 year history of difficulty rising from a seated position and increasing gait difficulty. Currently he demonstrates, a slow and wide-based gait, and constant facial grimacing. He is being treated with Sinemet (Carbidopa/Levodopa). Evaluation of this index patient led to the identification of 9 other employees at this shipyard who shared both a common exposure pathway to Manganese and Parkinsonism. *Conclusions:* Manganese exposure has been demonstrated to cause a neurologic syndrome that closely resembles Parkinson's Disease. Contrary to the Substantia Nigra involvement seen in Parkinson's Disease, manganese-induced Parkinson's Syndrome results from accumulation of the metal in the pallidum and striatum. Patients with both entities respond to Levodopa, as did our patient. MRI or PET scan imaging in patients presenting with Parkinsonism may be useful in identifying the etiology of the disorder. The importance of an occupational history is emphasized by finding others at risk in the same workplace setting. *References:* Olanow CW. Manganese-induced Parkinsonism and Parkinson's Disease. *Ann NY Acad Sci* 2004; 1012:209–223. March. Huang CC, Weng YH, Lu CS, Chu NS, Yen TC. Dopamine Transporter Binding in Chronic Manganese intoxication. *J Neurol* 2003; 250(11):1335–1339. Bulpitt CJ, Shaw K, Clifton P, Stern G, Davies JB, Reid JL. The symptoms of patients treated for Parkinson's Disease. *Clin Neuropharmacol* 1985; 8(2):175–183. Olanow CW, Good PF, et al. Manganese intoxication in the Rhesus monkey: a clinical, imaging, pathologic, and biochemical study. *Neurology* 1996; 46(2):492–498.

147. Repetition of Deliberate Self Poisoning

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Objective: To describe the incidence and epidemiology of repetition of self-poisoning by patients admitted to a hospital toxicology service. *Method:* Data collected by the Clinical Toxicology Service were used to review hospital admissions of adult patients (over 16 years) following deliberate self-poisoning during the 3-year period between January 2000 and December 2002. *Results:* There were 3797 episodes of self-poisoning during the study period involving 2982 patients. 408 (14%) patients were responsible for 815 (21%) episodes involving repetition of self-poisoning within the same calendar year as the index episode. Of the 408 patients repeating overdose within 1 year, 67% (274) had 2 admissions, 17% (64) had 3 admissions and 31% (127) had between 3 and 10 admissions in one year. The highest number of multiple admissions for a single patient during a one-year period was 33. There was yearly variation with 25% (327) episodes being repetitions in 2000, 22% (284) in 2001 and 17% (204) in 2002. Self-poisoning was more common amongst females who accounted for 54% of all episodes and 52% of episodes where overdose was repeated within a year. Mean age of those repeating overdose was 36.3 years in males and 33.6 years in females, compared to 33.9 years in males and 33.4 years in females who did not repeat. Episodes of repeated self-poisoning more frequently involved ingestion of multiple agents, 32% involving 3 or more agents compared to 25% episodes where overdose was not repeated. There was variation in the agents ingested. Of the episodes of repeat overdose 13% involved antipsychotic drugs, 25% benzodiazepines

and 5% tricyclic antidepressants. In cases where overdose was not repeated 6% involved antipsychotics, 15% benzodiazepines and 10% tricyclic antidepressants. Similar proportions of repeated and non-repeated episodes involved paracetamol (41%) and SSRI antidepressants (14%). Duration of hospital stay was 24 hours or less in 90% episodes whether or not there was repetition in the year. *Conclusion:* 21% of hospital admissions following self-poisoning involved repetition of overdose within a calendar year of a previous episode, higher than previously reported in the UK, although an increasing incidence of repetition has been observed (1,2). A small number of patients are responsible for a disproportionately high number of admissions. Males repeating overdose were older. Repeat overdoses more frequently involved multiple agents and ingestion of antipsychotic drugs and benzodiazepines. *References:* 1. Hawton K, et al. Trends in deliberate self-harm in Oxford 1985–1995. *Br J Psychiatr* 1997; 171:556–560. 2. Bialis MC, et al. Changing patterns of self-poisoning in a UK health district. *QJM* 1996; 89:893–901.

148. Factors Associated with Need for High Dependency Care in Patients Presenting with Poisoning

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Objective: Poisoning is a common reason for presentation to hospital. Most patients do not suffer serious morbidity and mortality is uncommon. In the UK few patients require admission to high dependency care, including the Intensive Therapy Unit (ITU), High Dependency Unit (HDU) or Coronary Care Unit (CCU). This study was performed to establish factors associated with an increased need for high dependency care. *Methods:* The computer records of all patients presenting to the Freeman Hospital Clinical Toxicology Service with poisoning between 2000 and 2003 were examined to identify patients who required admission to ITU, HDU or CCU care. Their clinical characteristics were compared with the remaining patients who did not require ITU admission. *Results:* There were 4,762 presentations during the period of study and 73 of these (1.5%) required high dependency care, usually because of a need for airway and respiratory support. There were no significant differences in the ages of patients comparing those who did and did not require high dependency care (median 32 y in both groups) and the proportions of females in each group were 55% and 54% respectively. Compared to patients managed in the general ward, patients requiring high dependency care were more likely to have been exposed to multiple agents (e.g. proportion exposed to 3 or more agents 37% vs. 28%, $P<0.001$) and to have been exposed to tricyclic antidepressants (53% vs. 8%, $P<0.001$), antipsychotic drugs (19.2% vs. 8.3%, $P<0.003$) or benzodiazepines (30% vs. 20%, $P<0.05$) and less likely to have been exposed to paracetamol (15% vs. 41%, $P<0.001$), SSRI antidepressants (4% vs. 14%, $P<0.001$) or NSAIDs (4% vs. 11%, $P<0.003$). There were no significant differences between the 2 groups in rates of exposure to alcohol, opioids, or illicit drugs, including heroin and ecstasy. Two patients (3%) needing high dependency care died. In the remainder, length of stay in hospital was 2 nights or more in 38 episodes (49%); all but one of these were discharged from hospital within a week of admission. *Conclusions:* The proportion of patients needing high dependency care, usually for airway and respiratory support, is small. In more than half of these, tricyclic antidepressants are involved. Benzodiazepines and antipsychotic drugs are also commonly involved. Prognosis in this patient group is good, with most being discharged from hospital within a few days.

149. Drug Overdose in the Elderly: Current Patterns of Presentation and Management in Newcastle, United Kingdom

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Objective: The elderly constitute a small but important fraction of patients presenting to hospital with drug overdose. This study was performed to provide contemporary data comparing the characteristics of episodes involving elderly patients with those affecting younger patient groups. *Methods:* A retrospective survey was carried out of all poisoning admissions to Freeman Hospital, Newcastle, between the years 2000 and 2003. The characteristics of episodes involving elderly patients (>65 years) were compared with those of patients aged 16–34 y and 30–64 y. *Results:* There were 4,762 poisoning admissions, 131 (2.8%) of these involved a total of 115 elderly patients. Comparing episodes in the elderly with those in the 35–64 y and 16–34 y groups respectively, there were no significant differences in the proportion of females (52.7% vs. 53.5% vs. 55.3%). Elderly patients were significantly less likely to have taken an intentional overdose and more likely to have had an accidental exposure (20% vs. 3% vs. 3%, $P<0.01$). Elderly patients were significantly less likely to have been exposed to alcohol (11% vs. 33% vs. 28%, $P<0.001$), SSRI antidepressants (6.9% vs. 14.7% vs. 14.5%, $P<0.001$) or NSAIDs (2.3% vs. 9.7% vs. 12.3%, $P<0.001$)

and more likely to have taken benzodiazepines (27% vs. 24% vs. 17%, P<0.01 vs. 16–64 y group) or cardiac drugs (11.5% vs. 5.8% vs. 3.0%, P<0.05). Elderly patients were more likely to present during the period 9 a.m. to 5 p.m. (33% vs. 19% vs. 17%, P<0.001); their average length of stay was increased with a higher proportion staying more than 1 night (23% vs. 11% vs. 9%, P<0.002), but there were no significant differences in the proportions admitted to intensive or high dependency care (0.8 vs. 1.4 vs. 1.7%). There were only 2 deaths, both in the 16–34 y age group. A lower proportion of elderly patients took their own discharge or absconded (2% vs. 15% vs. 18%, P<0.001) and more were transferred to in-patient psychiatric care (4.3% vs. 1.3% vs. 0.7%, P<0.05 vs. 16–64 y group). *Conclusions:* Poisoning as a result of intentional drug overdose continues to be uncommon in the elderly. As in an earlier series from this hospital (1), elderly patients have a higher prevalence of formal psychiatric disease as evidenced by the higher proportion admitted for further psychiatric care, and are more likely to take prescribed drugs. Although they have a longer hospital stay, this study provides no evidence for increased morbidity following poisoning. *Reference:* 1. Wynne H, et al. *Hum Exp Toxicol* 1988; 6:511–515.

150. Has Paracetamol Legislation Led to an Increase in the Use of Salicylates and Ibuprofen Analgesia in Overdose?

Walsh N, Donohoe E, Cooke A, Tracey JA. *National Poisons Information Centre, Beaumont Hospital, Dublin, Ireland.*

Background: Legislation controlling the sale of paracetamol in non-pharmacy retail outlets was introduced in Ireland in October 2001. This led to a significant decrease in the severity of paracetamol overdoses (1). *Objective:* We examined acute deliberate overdoses involving aspirin and ibuprofen to determine if there was any increase in these cases. *Methods:* We retrospectively examined Poisons Centre data on acute deliberate overdoses involving aspirin and ibuprofen during two 24 month periods before and after October 2001. These periods were compared using non-parametric t-test statistical analysis. *Results:* A total of 1,602 acute deliberate overdoses of aspirin and ibuprofen were reported to the Poisons Centre during the study period—885 before the legislation and 717 after the legislation. There was a significant drop in the total number of overdoses involving aspirin and ibuprofen (p=0.0479, 95% CI 0.07–13.93). There was a very statistically significant drop in the number of overdoses involving aspirin (p=0.0038, 95% CI 2.48–11.36). There was no change in the number of overdoses involving ibuprofen (p=0.8964, 95% CI—3.06–3.48). *Discussion:* Legislation introduced in October 2001 led to a substantial decrease in the number of paracetamol tablets taken in overdose. It has previously been shown that acute deliberate overdoses are often impulsive acts (2). The decreased availability of paracetamol may possibly lead to an increase in the use of other analgesics (3), for overdose. In Ireland aspirin and ibuprofen are over-the-counter drugs and are therefore readily available. We examined the incidence of overdose with these drugs before and after October 2001 and found no increase in their use. *Conclusion:* There has been no increase in the number of overdoses involving aspirin and ibuprofen reported to the Poisons Centre since the introduction of legislation controlling the sale of paracetamol in Ireland. *References:* 1. Walsh N, Donohoe E, Tracey JA. Smaller pack size has a positive impact on deliberate paracetamol overdose in Ireland. *J Toxicol Clin Toxicol* 2004; 42:499 [abstract]. 2. Hawton K, Ware C, Mistry H. Paracetamol self-poisoning: characteristics, prevention and harm reduction. *Br J Psychiatr* 1996; 168:43–48. 3. Balit CR, Isbister GK, Peat J, Dawson AH, Whyte IM. Paracetamol recall: a natural experiment influencing analgesic poisoning. *Med J Aust* 2002; 176(4):162–165. 4. Sheen CL, Dillon JF, Bateman DN, Simpson KJ, MacDonald TM. Paracetamol pack size restriction: the impact on paracetamol poisoning and the over-the-counter supply of paracetamol, aspirin and ibuprofen. *Pharmacoepidemiol Drug Saf* 2002; 11(4):329–331.

151. Does Weather Affect Self Poisoning?

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Objective: Many studies have attempted to investigate possible connections between the weather and attempted suicide with varying results. The aim of this study was to investigate the possible correlations between the number of admissions to the Welsh National Poisons Unit and local weather conditions between 1989 and 1999. *Methods:* Admissions data for self-poisoned patients was extracted from the WNPU database. For the purpose of this study the data were recorded as monthly and seasonal totals. The local monthly weather data was obtained from the Met Office for mean temperature, barometric pressure, sunshine amount, cloud cover and humidity. Rainfall data were obtained from the Hadley research centre website (England and Wales total) and the International Station of Meteorological Summary (Cardiff). Average monthly weather data were plotted against monthly admissions to determine any possible correlations. The individual monthly data for each year were also plotted. The same process was carried out for the seasonal admissions against seasonal weather data. *Results:* The scatter graph for total mean monthly

temperature shows a strong positive relationship with admissions (r=+0.77). However when monthly data were plotted separately for all of the years this correlation disappeared. The same was found for total admissions against average sunshine amount in hours (r=+0.62). This correlation disappeared when the individual months were plotted. No correlations could be found between admissions and barometric pressure or humidity. The comparison of total figures for cloud cover showed no significant correlation. No patterns could be determined for either of the sets of rainfall data analysed when plotted against monthly admissions. Seasonal associations could be found for temperature (r=0.959), cloud cover (r=−0.79), sunshine hours (r=0.74) and humidity (r=−0.65) however these associations disappeared when data for individual seasons were compared. No association could be found between seasonal admissions and rainfall or barometric pressure. *Conclusion:* Significant associations between admissions to the poisons ward and local weather conditions could not be established in Cardiff despite superficial correlations. The implication is that admissions due to poisoning is influenced by other factors, for example social, financial, religious, ethnic or religious. It is also possible that limitations regarding admissions including availability of beds, location with respect to A&E departments and absence of ITU facilities have an influence. A combination of these factors could be great enough to conceal any possible weather influences, or it may be that meteorological conditions indeed have no influence.

152. Unintentional Poisonings in Adults: The Hidden Epidemic

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Accidental poisonings in adults are generally considered an uncommon occurrence. Preliminary review of our poison centre data indicates that unintentional exposures can account for a significant percentage of adult poisoning depending on the age range. We undertook 1) to ascertain the causal circumstances of nonintentional adult poisoning, 2) to determine the frequency of occurrence and 3) to identify trends that can translate into prevention messages. All adult accidental poisonings reported to our Poison Centre from April 1 2003 to March 31, 2004 were identified (4760 cases). 4087 cases had sufficient documentation for analysis, with the remainder having incomplete documentation (255), coding errors (222), were irretrievable (145) or unrelated to exposure (51). Chemical exposures represented 61% (2481) of adult exposures, medications 30% (1248), food related 5% (199), bites 2% (78) and other 2% (81). There was a seasonal trend for chemical exposures but not for medications, with peaks in June, July and August and again in January–February. Routes of chemical exposure were primarily dermal (1051) and inhalational (906), with 331 ingestions. The balance was other/unknown. Spills and splashes as a result of the following circumstances: cleaning the house/garage (386), work related (417), working on/under a car (113), agricultural work (49), with the remainder having no specified activity (815) or miscellaneous circumstances. Products commonly involved in house cleaning were general or specialized cleaners (49%), bleaches (29%) and caustics (13%). Using chemicals in an enclosed space was a common cause of resulting in inhalational, dermal, and ocular chemical exposures accounted for 1793 cases inhalational exposure (267).Three concerning trends reflected ingested chemicals either mistaken for an edible product (303), mistaken for a therapeutic product (55) or siphoned (64). In 62% of cases in this category, the chemical had been transferred to a food/drink container. Responsible products were primarily soaps/detergents (28%) and bleach (20%) with the balance represented by a wide variety of other substances. Although adults in the 20–39 age range represent 41% of the adult population in our catchment area, they represent 63% of chemical exposures occurring during cleaning the house or garage. Women are more likely to be exposed than men, likely reflecting gender differences in cleaning practices or reporting bias. Although 40–59 and >60 year olds represent 40% and 19% of the adult population, they accounted for 29% and 8% respectively of adult chemical cleaning exposures. Potential prevention messages need to address practices associated with pouring chemical products, transferring chemicals into food/drink containers as well as the use of chemicals in an enclosed space with proper ventilation. These should be targeted to adults in the 20–39 age range.

153. Epidemiology of Acute Methemoglobinemia in a Pediatrics Clinic

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Objective: The aim of this study is to present the incidence of acute methemoglobinemia in children,the clinical and laboratory presentation and the evolution with treatment. *Methods:* We studied all the children with acute methemoglobinemia admitted in our clinic over a 5 years period (1999–2003).We analysed the age, sex, place of residence, clinical symptoms, laboratory data,

treatment methods and the hospitalisation period. *Results:* 82 patients with acute methemoglobinemia were admitted in The Pediatrics Clinic between 1999–2003.All the patients were from rural places or from the suburbs of the capital were there is not sewerage system.In all the cases the source of methemoglobinemia was draw well's water used to prepare children's food. The age distribution was as follows: 0–1 month: 19 cases, 1–3 months: 39 cases, 3–6 months: 12 cases, 6–12 months: 4 cases, 1–3 years: 8 cases. There were no patients more than 3 years old. There were 35 girls and 47 boys. All the 82 patients presented with sudden onset generalised cyanosis unresponsive to oxygen therapy;''chocolate-brown'' blood; metabolic acidosis and high levels of methemoglobinemia (10%–50% in 43 patients, 50%–70% in 33 patiens and more than 70% in 6 patients). In all the cases the patients received intravenous metylene blue: 1 ml/kg – 1:1000 solution and intravenous ascorbic acid 30 mg/kg. The medium hospitalisation period was 48 hours. 81 children recovered completely and were discharged. One death was reported involving a male infant, 4 months old. No rebound or escalating methemoglobinemia was reported in the 81 patients who recovered. *Conclusion:* Acute acquired methemoglobinemia is not a very rare cause of hospitalisation in infants and children up to 3 years old.In our country the source is still contaminated water from places without a sewerage system.The majority of the patients are up to 6 months old. Patients more than 1 year old probably have a congenital enzyme deficiency and need special investigations. *References:* 1. Ford, Delaney, Ling, Erickson. Clinical Toxicology 2001 Edition. 2. Ulmeanu, Oraseanu. Acute poisoning in children—diagnosis and treatment. Bucharest, 1995.

154. The Epidemiology of Poisoning in the Elderly Irish Population

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Objective: To characterise the incidence of poisoning in the elderly Irish population. *Methods:* A 3 year retrospective study of telephone enquiries to the National Poisons Information Centre (NPIC) was conducted from January 2001 to December 2003 inclusive. All cases concerning patients aged over 65 years were identified. Information on circumstance, patient age, sex, type of agent(s), clinical features, symptom severity, location of exposure, and route of exposure was collated. Patients were grouped according to age (65–69, 70–74, 75–79, 80–84, 85–89, 90–94, >95 years). Patients described as ''elderly'', ''retired,'' or ''in their 60's'' were excluded from data analysis. *Results:* During the study period, 1.9% of patient enquiries to the NPIC involved patients aged over 65 years (n=575), who met the study inclusion criteria. 54.4% of poisoning exposures in the elderly were unintentional/accidental, 37.2% were intentional, in 5.6% of cases the circumstances were unknown, and 2.8% were requests for information only. Patient age ranged from 65–98 years and poisoning was most prevalent in the 70–74 years age group. Females predominated in all age groups and the male-to-female ratio was 1:1.6. 70.3% of exposures involved poisoning with medication, 29.0% involved chemicals, and 0.7% foreign bodies. Cardiovascular drugs, hypnotic/sedatives, antidepressants, analgesics, and psycholeptic agents were the predominant pharmaceuticals implicated in poisoning, while the main chemicals included bleach, alcohol, pesticides/herbicides, corrosive chemicals, and denture cleaners. The majority of patients were either asymptomatic (n=210) or developed minor clinical features (n=234). Patients who took an intentional overdose were more likely to be symptomatic than those with unintentional/accidental poisoning (65.9% versus 40.45% respectively). 10 patients developed severe toxicity and 8 required admission to intensive care facilities. There were 5 fatalities; two deaths occurred following intentional poisoning, one death each occurred following unintentional poisoning and chronic toxicity respectively, and the circumstances were unknown for one fatality. Drowsiness, gastrointestinal upset, confusion/disorientation, haemodynamic changes, and bradycardia were the most common features reported. Most poisoning exposures occurred in a domestic setting (86.6%), while nursing home and hospital poisonings accounted for 4.5% and 4.2% of cases respectively. Ingestion was the principal route of exposure (91.7%), followed by inhalation (4.2%), eye (1.8%), skin (0.9%), intravenous (1.2%) and intramuscular exposures (0.2%). *Conclusion:* Significant morbidity and mortality are associated with unintentional and intentional poisoning in the elderly. Poison prevention strategies emphasising chemical safety, appropriate drug use, and regular review of prescribed medication are needed to reduce toxic exposures in elderly patients.

155. Morbidity and Mortality of Acute Poisonings in Norway 1999–2002

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Objective: In Norway (4.5 million inhabitants) there is lacking information regarding statistics on morbidity and mortality of acute poisonings on national level. The aim of this study is therefore to map the exact number of patients with morbidity and mortality associated with acute poisonings in Norway, 1999–2002. *Methods:* For this study morbidity was defined as patients admitted in Norwegian hospitals due to acute poisonings. We collected morbidity and mortality data from the Norwegian Patient Register (NPR) by using the following codes: T4n-T65.0 and F10.0-F19.0 (ICD-10). The coding was done locally at each hospital using one main diagnosis and 7 side diagnoses. Mortality data (in- and outside hospitals) was also extracted from The Norwegian Causes of Death Register (NCDR) using the same ICD-10 codes. These data are based on medical death certificates issued by a physician. Each death in the NCDR is classified centrally. *Results:* Morbidity (data from NPR): The mean annual number of patients admitted to hospital with the diagnosis acute poisoning (both main- and side diagnosis) was 10,238 (8924–11855). Almost 80% was due to drugs and biological substances (T4n-T65.0) and almost 20% was due to acute poisoning with alcohol in patients with mental and behavioural disorders (F10.0). 82,3% were between 15–59 years old and 51,9% of the patients were women. Mortality in hospital (data from NPR): Of the 10 238 patients admitted to hospital in average per year, only 98 (87–111) were discharged as dead. 56,9% were between 15–59 years old and 40% were women. Almost 90% was due to drugs and biological substances and 10% was due to acute poisoning with psychoactive substances in patients with mental and behavioural disorders (F10.0-19.0). Mortality in and outside hospital (data from NCDR): 500 (429–576) deaths in average per year were registered. 90,9% were between 15–59 years and 27,3% were women. In this group the majority (58,5% in average) was registered with one of the F-codes (F10.0-19.0). *Conclusion:* Unfortunately, our data seem to be encumbered with some uncertainties due to varying coding practice and poor quality assurance. The number of deaths from acute poisoning in Norway (in- and outside hospital) is about 5 times higher than the number of deaths recorded in hospital. The morbidity and mortality of poisonings in Norway seems to be low compared to most other European countries.

156. Patterns of Intentional Self-Poisoning in Adults

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Objective: To describe patterns of intentional self-poisoning by patients admitted to a hospital toxicology service. *Method:* Data collected by the Clinical Toxicology Service were used to review hospital admissions of adult patients (over 16 years) following deliberate self-poisoning during the 3-year period between January 2000 and December 2002. *Results:* 3797 admissions occurred during the study period. Females accounted for 54% admissions (episode-based female to male ratio 1.17:1). Mean age was 34.1 years, with peak incidence in the 20–34 year age group, differing from earlier data which identified peak incidence in the 15–24 year age group 1. Peak age was 25–29 years for males and 20–29 years for females. On average 21% episodes represented repetition of overdose within 1 calendar year. A daily pattern of admissions occurred with fewest between 07.00am and 09.00am and most at 01.00am. 25% admissions occurred between 00.00 hrs and 04.00am. More admissions occurred at the weekend, with 14.7% on Friday, 14.4% on Saturday and 16% on Sunday, with an even distribution throughout the remaining days. The highest number of admissions occurred during March (9%), April (10%) and October (9%), with the lowest number in September (7%) and January (6%). A trough in admissions occurred during September in all years for males and females. In all years a peak in female admissions occurred during March and April with a trough in May, which was not observed amongst males. 39% episodes involved ingestion of a single agent, 33% 2 agents and 28% 3 or more agents. Paracetamol was implicated in 41% episodes, non steroidal anti-inflammatory drugs (NSAIDs) in 10% and opiate analgesics in 21%. SSRI antidepressants were taken in 14% episodes, tricyclic antidepressants in 8.8%, benzodiazepines in 18% and antipyschotic drugs in 8%. Alcohol was ingested in 29% and illicit drugs in 9% cases. Comparison with earlier data shows similar use of paracetamol and benzodiazpines and increased use of SSRIs, NSAIDs and illicit drugs1. Duration of hospital admission was 24 hours or less in 90% of episodes. In 81% of episodes patients were discharged from medical care. 1% of admissions resulted in transfer to psychiatric care, 5% absconded and 11% self-discharged against medical advice. Inpatient mortality rate was <0.3%. *Conclusion:* Peak age for self-poisoning was older than previously reported and some changes in agents used have occurred. Self-poisoning is more common in females and a seasonal pattern of female admissions may exist. Duration of hospital admission was brief and inpatient mortality low. *Reference:* 1. Thomas SHL, et al. Presentation of poisoned patient to accident and emergency departments in the North of England. *Hum Exper Toxicol* 1996; 15:466–470.

157. Scopolamine Treatment for Organophosphate (Chlorpyrifos) Ingestion

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Objective: The use of competitive inhibitors of acetylcholine other than atropine for patients with organophosphate poisoning is controversial. As scopolamine has a greater capacity than atropine to cross the blood brain barrier, it has been suggested that it should be used in patients with organophosphate poisoning who have central nervous system manifestations. *Case Report:* A 17 years-old girl was admitted to the pediatric ward after ingesting chlorpyrifos in a suicide attempt. She reported vomiting three times. She had no other symptoms for 12 hours and than over the course of 36 hours gradually developed extra-pyramidal signs and became comatose. She was treated with intravenous scopolamine. Within three minutes the patient started to respond to verbal commands and answered simple questions, rigidity subsided and she was able to sit up in bed. She was discharged after four days with no neurological sequelae. *Conclusions:* We suggest that in patients with organophosphate poisoning who have mainly central nervous system toxicity scopolamine administration might be considered.

158. Acute Accidental Piperonyl-Butoxide Intoxication After Percutaneous Absorption: Case Report

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Objective: Piperonil-butoxide (PB) is in wide use as a pesticide synergist. PB increases the insecticidal potency of pyrethrins, carbamates and occasionally other classes of insecticides. PB is considered relatively harmless in humans, and in some countries is used as a food additive. *Case Report:* A previously healthy man of 63, preserved the wooden roof construction of his house with an insecticide that contained 94.8% PB. He used an improvised mask over the nose and mouth. After half an hour of work he felt weakness and dizziness. With effort he managed to go out on a fresh air. Ten minutes later, he experienced nausea and vomited once. He took a bath and washed his hair. He presented at the toxicology department via ambulance 1.5 hours after exposure. On admission he was alert and orientated and complained of moderate weakness. Clinical examination revealed sinus bradycardia of 50 beats per minute with minimal elevation of ST segment in leads I, II, III, AVF,V4-6. There were no other abnormalities. Toxicological analysis of serum revealed the presence of piperonal, which is a PB metabolite. The patient was admitted and placed on ECG monitoring. Within 24 hours the bradycardia and all other symptoms resolved. *Conclusion:* We believe that patient's symptoms and signs, including cardiac disturbances, were toxic effects of PB. It is well known that PB has good percutaneous absorption. In our opinion, in this case, PB was absorbed mostly through the skin. Bradycardia after exposure to PB in a previously healthy man, as well as toxicological confirmation of PB metabolite in blood, indicate its cardiotoxic potential. From this report is obvious that PB, although considered as relatively harmless for humans, can cause serious disorders.

159. Toxicity of Creosote and Related Products

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Objective: Creosote is a mixture of aromatics and phenol. Phenol compounds are used in the chemical industry, as medical and veterinary antiseptics, disinfectants, reagents and preservatives. Old sleepers processed with creosote have been recycled in public and private gardens for decoration and for making outdoor furniture and swings for children. An European Commission directive, C(2001) 3227, prohibits the marketing of creosote as a wood preservative because of its potential carcinogenicity; Directive 2001/91/UE prohibited the use and marketing of creosote treated wood and was incorporated in Spanish legislation in 2002. As a result many institutions called our centre for advice. Therefore we decided to examine the circumstances of creosote exposure and consults to the SPCC. *Methods:* Review of medical records of phenol related compounds registered to the SPCC. Over-the counter preparations or pharmaceuticals such as analgesic preparations were excluded. Extracted data included routine demographics, aetiology and clinical features. Consults about creosote processed wood are also studied. *Results:* We recorded 527 consults due to exposures to creosote and phenol products during the last 13 years. The products were used as disinfectants in 73.6% of cases,

solvents in 9.5% or in agrochemicals with lindane in 7.6%. There was one commercial compound containing concentrated creosote which accounted for 70.8% of all cases. There was a predominance of males (male:female ratio 2:1) and adults were 63.2% (mean age: 37 years old). The rest were children with a mean age of 24 months (range 10 months–14 years). Phenol compounds were the only substance involved in 96.6% of cases. Reasons for exposure were the following: unintentional-general 71.7%, occupational 14.4%, intentional suicide 8.3%, and others 5.6%. 56% occurred in a residence, 12.5% in the workplace, 4.2% in nature, 0.8% at schools, 0.8% in penitentiary institutions and 25.7% in other places. The majority of exposures were oral (52.6%), followed by inhalation (17.3%), dermal (14.2%), ocular (9.8%), and several routes (6.1%). Symptoms reported were gastrointestinal 87 cases, neurological 31 (coma 13, convulsions 5) after ingestion, skin burns 27 and systemic symptoms 7 after dermal exposure and systemic pathology (including neurological and hepatotoxicity) 64 after inhalation. Subsequent activities of the SPCC related to creosote included written consultations by authorities about old sleepers preserved with creosote and reused in parks in 4 occasions, and by the general public in 12 occasions. *Conclusions:* Products containing creosote have many risks to human health and their use should be restricted to professionals. Publicity of the Directive and implementation of their recommendations are needed. Official agents should look for alternatives for the upkeep of outdoor ornamental wood, remove the existing sleepers and swings and warn the population and state bodies about ornamental use in public and private gardens.

160. Quantitative HPLC Analysis of Diuron and Three Metabolites in Human Serum and Urine

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Objective: Diuron (1-(3,4-dichlorophenyl)-3,3-dimethylurea) is a substituted urea-herbicide. A validated HPLC-DAD method to quantitate diuron and its metabolites, (3,4-dichlorophenyl-3-methylurea, 3,4-dichlorophenyl-urea and 3,4-dichloroaniline) in human serum and urine is presented. The method was applied to an intoxication case involving unsuspected diuron intake. *Methods:* A simple liquid–liquid extraction with dichloromethane is used for sample clean-up. The compounds are separated on a μBondapak C18 column using a mobile phase of KH2PO4/CH3CN (65/35, v/v, pH3) at a flow-rate of 1.0 mL/min. The display wavelength is 245 nm. *Results:* Linear calibration curves were obtained in the concentration range from 50 to 1000 ng/mL for all compounds. Within-day and between-day VC% were <10% and <15% at two different concentration levels. The LOQ of all compounds was 50 ng/mL serum or urine. The concentrations of 3,4-dichlorophenyl-3-methylurea and 3,4-dichlorophenyl-urea were highest in the patient plasma and urine samples, while diuron and 3,4-dichloroaniline were only found in trace amounts. Total concentrations were found to be near 150 mg/L in serum and 250 mg/L in urine. The patient fully recovered. *Conclusion:* The described HPLC method allows for a quick and sensitive analysis of diuron and its metabolites in blood and urine. The results of the patient samples show that the major route of metabolism in man is demethylation. These findings are in agreement with earlier reports (1,2). *References:* 1. Verheij E, van der Greef J, La Vos G, et al. Identification of diuron and four of its metabolites in human postmortem plasma and urine by LC/MS with a moving-belt interface. *J Anal Toxicol* 1989; 13:8–12. 2. Van Boven M, Laruelle L, Daenens P. HPLC analysis of diuron and metabolites in blood and urine. *J Anal Toxicol* 1990; 14:231–234.

161. Organophosphorus Induced Delayed Neuropathy (OPIDN). Report on Eight Cases

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Background: Single doses of certain organophosphorus (OP) compounds (phosphates, phosphonates and phosphoroamidates) cause OPIDN which is characterized by degeneration of long and large diameter axons in the central (C) and peripheral nervous system (PNS). In the PNS, the most frequent clinical manifestation is a sensoriomotor polyneuropathy. *Objective:* To present eight cases of acute OP poisoning in whom OPIDN was diagnosed. *Method:* We studied acute cases of OP poisoned patients attending the UNICAMP Poison Control Center that developed neuropathy, and in whom was possible to exclude other concomitant causes such as diabetes, alcoholism, or porphyrias. *Case Series:* Table 1 summarizes the main information of 8 cases of OPIDN attributed to exposure to OP. Eight patients presented from December 1985 to October 2004 with acute poisoning by methamidophos (4 cases), trichlorphon (Neguvon) (3 cases) and one by an unidentified OP. Three patients were female and five were males. Age ranged from 19 to 40 years. Duration of hospital admission was 9 to 30 days. Six patients

TABLE 1

Year	Age/sex	Days in hospital	Time from exposure to onset (days)	Follow up	Involved product	Clinical OPIDN	ENMG
2004	40F	30	13	50d	Methamidophos	PNS	PNS+
2003	38M	20*	20	2m	Methamidophos	C+PNS	PNS+
2003	28M	12*	22	1y	Methamidophos	PNS	PNS+
2003	19F	22	25	3m	Methamidophos	MND	MND
2002	23M	16	16	9m	Trichlorfon	PNS	ND
2001	28M	21	21	3y	OP	PNS	PNS+
1986	36M	21	21	18m	Trichlorfon	PNS	ND
1985	32F	9	9	5m	Trichlorfon	PNS	ND

MND=alfa motorneurone disease; ND=not done.
*Cardio-respiratory arrest (CRA) on admittance.

ingested poison in suicide attempts, one by accident, and one was an occupational accident. The time from exposure to onset of neuropathic manifestations ranged from 9 to 25 days. Two case who had CRA promptly recovered. Except for two cases attending in 1985 and 1986, the other six occurred between 2001 and 2004. The follow up ranged from 50 days to three years, but five are still under observation. An electrophysiological study (ENMG) was performed at leat once in 5 patients. Four patients had a sensory-motor neuropathy, with motor predominance. One patient had ENMG features of alfa motorneurone disease. *Comment:* In our series, sensory and motor polyneuropathy predominates, but a case of MND was documented. Sensory-motor neuropathy was always of motor predominance.

162. Paraquat Exposures: Are Still a Serious Problem in Spain

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Background: Paraquat pesticide can produce pulmonary fibrosis, skin and gastrointestinal burns, hepatitis, and renal failure. Pulmonary fibrosis is the main cause of death. The aim of this study was to examine the severity of paraquat intoxication depending on the exposure aetiology. *Methods:* All paraquat exposures registered in our Poison Control Centre were evaluated retrospectively, from January 1991 to September 2004. Age, gender, aetiology, exposure routes, clinical manifestations, and severity of symptoms were registered. *Results:* There were 517 paraquat exposures. Occupational aetiology was in 48.1% of cases, accidental in 29.2%, intentional in 19% of occasions, and unknown in 3.7% of cases. *Occupational Poisonings:* 94.4% were male, 4.8% female, and for 0.8% the sex was unknown. All cases were adults. The exposure routes were the following: oral in 6.4% of patients, dermal in 40.5%, inhalation in 41.1%, ocular in 6.3%, and other routes in 5.6% of cases. 4.8% of exposures were asymptomatic. Mild clinical effects occurred in 39% of patients, moderate in 43.4%, severe in 10.8%, and death in 0.8% of cases, and in 1.2% clinical details remained unknown. *Intentional Poisonings:* All cases were adults. Of the 98 examined cases 81% were male, 17% were female, and in 2% the sex was unknown. Exposure routes were the following: oral in 96% of cases, intravenous in 3%, and intramuscular in 1% of exposures. Moderate clinical effects were observed in 13.2% of the cases, severe in 55.4% and fatal outcomes in 24.4%, and unknown in 7% of these intentional exposures. *Accidental Poisonings:* Children accounted for 17.3% of cases, adults for 65.5%, and 17.2% the age was unknown. 76.9% of these exposures involved males, 20.5% females, and in 2.6% the sex was unknown. Exposure routes of accidental poisonings were the following: oral in 39.7% of cases, dermal in 23.8%, inhalation in 24.5%, ocular in 8%, and mouth mucous membrane in 4% of patients. Six percent of cases were asymptomatic, mild clinical effects were present in 31% of patients, moderate effects were in 38% of cases, severe effects appeared in 15% of cases, death in 4% of patients, and this was unknown in 6% of occasions. *Conclusions:* Adult, male, and intentional exposure are the characteristics more frequently involved in severe cases. The exposure routes are directly related to aetiology except in accidental poisoning; the oral exposure is more frequent in intentional exposures, and inhalation-dermal contact at workplace exposures. Prognosis is worse in intentional exposures followed by accidental and occupational exposures.

163. Use of Qualitative and Quantitative Methods for Paraquat Determination as Decision Aid for the Treatment of Paraquat Poisoning

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Objective: Timely measurement of paraquat in plasma is important to assess severity and to decide on treatment in cases of poisoning (1). There is a need for simple sensitive non-instrumental tests for paraquat that can be carried out in non-specialised laboratories. *Methods:* Paraquat forms a blue colour with sodium dithionite under alkaline conditions in a highly specific reaction and a simple urine test can confirm the presence of paraquat (detection limit approx. 1 microgram/mL). The sensitivity of the reaction can be improved by using an adsorption cartridge onto which paraquat has been trapped (2). This test has been improved and simplified. *Results:* A recommended strategy for analysis of paraquat involves separation of plasma from 10 mL of blood. In a pre-screen 0.9 mL of plasma is mixed with 0.1 mL dithionite reagent in a small glass tube. A blue colour confirms the presence of paraquat above 2 microgram/mL. If the test is negative or inconclusive then 3 mL of plasma is loaded onto a 3 mL capacity cartridge containing 20 mg of silica. and washed with water. Dithionite reagent is added and if paraquat is present a blue band appears within 1 minute (detection limit approx. 0.1 microgram/mL). A similar test can be used for urine, which is made alkaline before loading onto the cartridge. With a 10 mL sample, 0.05 microgram/mL can be detected. Urine measurements can also be useful in assessing the severity of intoxication (3). The tests can be made semi-quantitative by reference to photographic dose response charts. For quantitative analysis down to 0.05 microgram/mL a simple UV spectroscopic method is available based on trapping paraquat from plasma onto a 4 mg silica microcartridge, followed by recovery in 200 microlitres of dithionite reagent into a microcuvette. For the highest sensitivity analysis down to 0.5 nanogram/mL, paraquat is oxidised to the dipyridone derivative and determined by HPLC with fluorescence detection. *Conclusion:* These methods can be applied to the diagnosis of paraquat exposure in a clinical setting. The choice will depend on the need for analytical sensitivity, equipment availability and the speed with which a result is required. *References:* 1. Proudfoot AT. Diagnosis and management of acute poisoning 2nd Ed., 1982, Butterworth Heinemann. 2. Woollen BH, Mahler D. An improved spot test for paraquat and diquat in biological samples. *Clin Chim Acta* 1987; 167:225–229. 3. Bismuth C, Hall AH. Paraquat poisoning, 1995, Marcel Dekker.

164. Propofol in the Symptomatic Treatment of Myoclonic Myoclonus Syndrome Induced by Chloralose Poisoning

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Objectives: Severe poisoning with alpha-chloralose may induce coma and hyperexcitability with generalised convulsions and myoclonic jerks. Benzodiazepines are usually considered to control myoclonus syndrome. Propofol, one of the most commonly used parenteral anesthetic, was suggested in one case report as an alternative treatment if other anti-epileptic treatment failed (1). *Methods:* Case report with discussion of the potential interest of propofol in the treatment of poisoning-induced resistant generalised convulsions. *Results:* A seventeen-year-old woman without significant medical past or psychiatric history was admitted in our intensive care unit because of an alpha-chloralose poisoning. She had ingested 190 g of alpha-chloralose and was found comatose with generalised convulsions. She was intubated and sedated using 250-mg thiopental and 10-mg/h midazolam continuous infusion. Following 1-g fosphenytoine and 2-mg clonazepam IV bolus and despite 2-g daily thiopental continuous infusion, generalised convulsions were still recorded on electroencephalogram. Thiopental treatment was thus discontinuated and 100-mg/h propofol infusion started, resulting in the resolution of the status epilepticus. Forty-eight hours after admission, propofol was stopped and the patient awaked without convulsion movements. Trachea was extubated and the patient discharged 7 days later without neurological sequelae. *Conclusions:* Propofol could be used in case of failure of usual anticonvulsive treatments in chloralose poisonings. Its place in the symptomatic arsenal of poisoning-related seizures is unknown and should be investigated. Although its anticonvulsivant effects are discussed, with some data even suggesting proconvulsant activity when combined with other drugs (2), propofol's efficacy as neuroprotectant should be more largely discussed in acute intoxication. *References:* 1. Quinio P, et al. *Anesthesiology* 1995; 83:875. 2. Modica PA, et al. *Can J Anaesth* 1992; 39:236–241.

165. Central Nervous System Depression, Acute Respiratory Insufficiency and Alterations in Heart Rate Associated with Glufosinate Poisoning

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Objective: We report the case of a patient with CNS depression, respiratory insufficiency and alterations in the heart rate, after the ingestion of a toxic dose of glufosinate. *Case Report:* A 41 year-old women, suffering an anxious-depressive syndrome, was sent to the emergency unit of our hospital after ingesting around 50 ml of a herbicide (Finale) containing 15% of glufosinate 12 hours previously. On admission, the clinical signs were normal except for a sinus bradycardia at 43 beats/minute. The physical examination was normal. Gastric lavage was carried out, with the administration of 25 g of activated charcoal, and the patient was admitted for observation. Thirty hours after ingestion, there was a progressive loss of consciousness (Glasgow Coma Score of 8), with hypoxemic respiratory insufficiency and the appearance of pulmonary infiltrates. The patient was intubated and mechanical ventilation was begun. At 48 hours after ingestion, the patient suffered several self-limiting episodes of ventricular tachycardia, with no hemodynamic repercussions, and was treated with amiodarone. No hydroelectrolytic changes or alterations of hepatic, renal or muscular biochemical parameters were observed. Tests of the mitochondrial respiratory chain showed that the enzymatic activity of complexes 2, 3 and 4 of the cytochrome-oxidase was normal. Serum acetylcholinesterase activity was also normal. The neurological evolution was favourable and the patient recovered consciousness 24 hours later. The respiratory insufficiency improved rapidly and was attributed to bronchoaspiration. Mechanical ventilation was stopped at 48 hours. There was persistence of sinus bradycardia of 50–55 beats/minute and isolated ventricular extrasystole until 8 days after ingestion. The patient was finally discharged with a normal ECG and no sequelae. *Conclusion:* Glufosinate can cause alterations in the heart rate, CNS depression, and respiratory insufficiency in the probable context of bronchoaspiration. Clinical and ECG monitoring is warranted for a minimum of 48 hours after ingestion of glufosinate. *References:* Lawson R, Estrade-Chapellaz E. Intoxication volontaire par le glufosinate. *Ann Fr Anesth Réanim* 1999; 18:1025–1026. Koyama K, et al. Cardiovascular effects of a herbicide containing glufosinate and a surfactant: in vitro and in vivo analyses in rats. *Toxicol Appl Pharmacol* 1997; 145:409–414.

166. Pesticide Exposures, UK and Ireland April–Sep. 2004—Results of a Surveillance Project

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Objectives: To investigate the nature of pesticide enquiries to a UK National Poisons Information Service and Internet clinical toxicology database. *Background:* Public perception is that pesticide exposures cause morbidity but few cases are reported to the relevant authorities. Better surveillance may help to quantify this problem. *Methods:* All pesticide enquiries to the NPIS, Edinburgh telephone enquiry service were followed up by a postal questionnaire to obtain further details about the incident. All accesses to pesticides of interest (174 pesticides and products) on TOXBASE (UK clinical toxicology database) for the same period were automatically notified to NPIS, Edinburgh in real time as part of a pilot project. Users accessing these pesticides for a patient related enquiry completed on-line forms or a postal questionnaire. *Results:* For the period 1 April to 30 September 2004 24 telephone enquiry follow-ups, 159 electronic follow-ups and 286 postal follow-ups were available for analysis (469). Where gender was known, exposures involved 244 males (53.6%) and 209 females (45.9%). Age ranged from <1–84 years (median 13 years; 43.1% <5 years). There were 14 animal exposures (12 dogs, 2 cats). Most exposures were acute (442, 94.2%) and involved home/garden products (331, 70.6%). Exposures involved patient use (110, 23.5%), other person use (66, 14.1%), later exposure e.g. wood preservatives or rat poison left in a room (81, 17.3%), unsatisfactory storage (75, 16.0%) and occupational use (34, 7.2%), remainder unknown. Only 157 (33.5%) were definite exposures, the remainder were possible or unknown. Thirty-two, (6.8%) were due to deliberate self-harm. Ingestion alone was involved in 220 exposures (46.9%), skin contact 68 (14.5%), inhalation 57 (12.2%), eye contact 28 (6.0%) and multiple routes of exposure in 80 cases (17.1%). Most patients were not admitted or were discharged on the same day, 11 on the following day and 9 (1.9%) later (maximum stay 6 days). Most frequent exposures involved permethrin, paraquat, glyphosate, malathion (often lice preparations), metaldehyde, diquat, creosote, borax, sodium chlorate and bendiocarb. Childhood exposures were most commonly to insecticides, slug pellets and rodenticides. Overall in 248 cases (52.8%) there were no symptoms; in children (<13 years; 224) 183 (81.7%) had no symptoms. 13 patients required ventilation or intensive care and 5 died, all after paraquat ingestion (2 accidental, 3 deliberate). *Conclusions:* In the UK and Ireland, most pesticide exposures do not result in serious problems but paraquat, ingested either accidentally or deliberately does result in deaths.

167. Voluntary Acute Poisoning with Rodenticide Anticoagulant: A Retrospective Study

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Background: Rodenticide intoxications are frequent. Accidental poisonings in children are generally mild and require no treatment. In adults, intoxications are frequently severe because of the large amount ingested in a suicidal attempt. *Methods:* Retrospective study of calls for rodenticides collected by the Poison Center of Strasbourg from January 2000 to September 2004. *Results:* Of the total of 34805 calls to the Poison Center during this period, 279 calls (0.8%) were for rodenticide, among which 118 (42%) for rodenticide anticoagulants. Among these cases, 68 were accidental mild poisonings in children with grain-based baits or pellets. 4 calls were identified as accidental poisonings in adults, with one percutaneous. 46 adult deliberate self-poisonings were notified, among which one criminal and three not confessed (confirmed by toxicological analyses). Among this population, the mean age was 40 years old with a sex ratio of 1.4 (M/F). The molecule ingested was, by order of frequency, chlorophacinone, bromadiolone, difenacoum, coumatetralyl, unknown in 14 cases. The amount of rodenticide anticoagulant ingested was generally unspecified. The delay between the ingestion and the call was longer than 24 hours in 16 cases. The symptoms were: none (22 cases), abdominal pain (7 cases), bleeding (12 cases: melaena, hematuria, epistaxis, gingivorragia, excessive vaginal bleeding). In 12 cases, the prothrombin rate was $<10\%$. Among these cases, 9 were diagnosed late (delay >7 days), all the patients with bleeding, after ingestion of anticoagulant concentrate in oil. The treatment included: gastric lavage (3 cases), activated charcoal (3 cases), plasma coagulation factor infusion (9 cases), phytomenadione (20 cases). The length of antidotal administration was unknown in 11 cases, between 7 and 45 days in 9 cases. One death was reported, but without relation to poisoning (defenestration). *Conclusion:* Of 46 deliberate rodenticide anticoagulant intoxications, 12 were severe with bleeding and decrease in coagulation factors, due to long acting anticoagulant.

168. The Role of Our Poison Centre in the Treatment of Suicide Cases

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Background: In Hungary the number of suicidal attempts is estimated at 20,000 per year. Our department set up in 1947 is the only poison centre in Hungary and provides medical care for 3 million inhabitants in Budapest and its agglomeration. *Objective:*

TABLE 1

	1983	1988	1993	1998	2003
Patients	10,223	8,964	8,561	8,344	8,392
Males/females	4,601/5,622	3,854/5,110	3,938/4,623	3,588/4,756	3,788/4,604
Suicide/no suicide	8,893/1,330	7,244/1,720	7,333/1,228	6,997/1,347	7,188/1,204
Mortality	401 (3.92%)	218 (2.43%)	129 (1.51%)	133 (1.59%)	116 (1.38%)
Average time of hospitalisation (days)	3.67	3.43	2.96	2.48	2.11
The 5 most frequent causes of poisonings	Barbiturates	Sedatohyp.	BZD	BZD	BZD
	Fenothiazines	BZD	Sedatohyp.	Alcohol	SSRI
	BZD	Fenothiazines	CA	SSRI	Alcohol
	CO	Alcohol	Alcohol	Carbamazepine	CA
	Pesticides	Pesticides	Antipsychotics	CA	Beta-blockers
Therapy					
Antidote	ND	ND	716	759	748
Gastric lavage	ND	2677 (29.8%)	2491 (29.1%)	1449 (17.4%)	1426 (16.9%)
Extracorporal elimination					
Number of patients/treatments	ND	ND	103/281	127/268	114/273
Number of telephone calls for information about poisonings	ND	ND	ND	About 450	About 1200

ND: no correct data, BZD: benzodiazepines, CO: carbon monoxide, sedatohyp.: sedatohypnotics (meprobamat, glutethimide etc.), CA: cyclic antidepressants, SSRI: selective serotonin reuptake inhibitors.

To survey the efficacy of our special toxicological therapy and that of our information call service taking the statistics of our department for the last 20 years into consideration. Patients and methods: Data of patients treated at our department in 1983, 1988, 1993, 1998 and 2003 were analysed retrospectively. *Results:* see Table 1. *Conclusions:* During the last 20 years the number of patients attempting suicide gradually decreased in a similar manner to the non-intentional intoxication cases. However, the number of drug abusers has suddenly increased since the political changes of the late 1980s. The introduction of more and more up to date treatment methods conforming to the international protocols as well as the development of our information call service and the use of less toxic medicines in psychiatric practice resulted in a considerable decrease in mortality.

169. Acute Poisonings Related to Suicide Attempt in Old People: Management and Outcome in a Toxicological Intensive Care Unit

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Objectives: Increase of suicide attempts in the old persons may be attributed to the prolongation of life expectancy of those suffering from chronic and painful pathologies or disabilities, the increase of isolated person number, and the progression in the public opinion of ideas of life-and-death choice. The objectives of our study were to evaluate the management and outcome of intentional poisonings in old patients admitted to an intensive care unit. *Methods:* Collection and analysis of clinical, psychiatric and toxicological data of acutely poisoned patients admitted in our toxicological ICU, over a 6-year period (1998–2004); evaluation of the decisions of withholding and withdrawal of life support; expression of the results as % or median [extremes]. *Results:* Among 119 poisoned patients aged of $\geq$75 years admitted to our ICU, 64 patients (48F/16M, age: 81 years [75–96], MacCabe 2: 49%, SAPS II: 37 [8–91]), were admitted following a suicide attempt and were included in the study. The 55 others were admitted in relation to an accidental overdose and were excluded from this analysis. Autonomy was mildly (32%), moderately (28%), importantly (19%) or totally limited (9%). There was a depression (63%, including 3 patients with a past suicide attempt) or a significant medical (67%) past history, including heart failure (18/64), hemiplegia (6/64), cancer (8/64), home oxygen therapy (3/64), dementia (3/64) or chronic renal insufficiency (2/64). Their medical treatment included 5 different drugs [2–13]. No reaction to any recent event could be found (42%), while a pathological mourning (13%), an incapacitating pathology (12%), or a conjugal or familial conflict (9%) was indicated as the cause of the suicide attempt. The most frequently involved toxicants were benzodiazepines (61%), antidepressants (19%), cardiac glycosides (13%), and barbiturates (10%). On admission, 36/64 (60%) were found comatose at home (with a Glasgow Coma Score of 8 [3–15]) and 26/64 (41%) were intubated and mechanically ventilated. Among the patients, 28/64 (44%) developed an acute respiratory failure, 41/64 (64%) hypotension, and 12/72 (19%) an acute renal failure. 34/64 patients (53%) received antidotes: flumazenil (21/64), anti-digoxin Fab (4/64), naloxone (3/64), and catecholamines (7/64). Three patients (5%) died, following life support withholding. All survivors were able to return back home. *Conclusions:* ICU mortality rate of patients aged of $\geq$75 years following suicidal drug ingestion remains low (5%), regarding their general status and associated co-morbidities. Admission to ICU of very-old poisoned patients should not be restrictive. In our experience, consensual decision of life support withholding was undertaken in only 5% of the cases.

170. A Collaboration Experience of the Poison Control Centre with the Manufacturers

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Objective: A pioneer agreement between the Association of Surfactants and Detergents Manufacturers and the Spanish Poison Control Centre (SPCC) was carried out in 1988. The companies voluntarily informed the SPCC of their product compositions and included the SPCC phone number in the labels. Eleven years later, the Spanish Act RD 770/99 introduced compulsory and confidential notification of new cleaners and detergents and of alterations of their compositions. The data to be submitted include name of the product, classification according to the Directive 45/99/EU, and quantitative composition in a percentage range except for substances classified as ''Very toxic,'' ''Toxic'' or ''Corrosive,'' for which the exact percentage is asked. Three pharmacists select, prepare and process the documentation and electronically introduce the data in a user friendly way.

The inclusion of the PCC phone number in the labels is obligatory. The results of this experience are described here. *Methods:* The cleaner and detergent file database was queried retrospectively for 5 years. Records for patients exposed to detergents and cleaners in one year were reviewed. Data examined were the treatment advised by the SPCC including referring to a health care unit. *Results:* Since 2000, 33,330 cleaners and detergents notifications were sent by the manufacturers of which 90.1% were new products and the rest, modifications of previously registered formulations. A percentage of 67.4% of notifications were industrial products and the rest domestic cleaners. An example of toxicological interest was that of floor crystallisers/floor polish which can contain hexafluorosilicate, oxalic acid or only acrylic polymers. Direct contact with those responsible for marketing permitted the change of the design of labels in household cleaners confused with food or pharmaceutical products in several occasions. In addition a number of 10,688 of notifications were products not included in legislation such as solvents or paints with very different chemical compositions. During the year 2000, 32,421 cases of intoxications were registered in the SPCC. Cleaner and detergent ingestions were 10,405 (32.1%) and 8,217 of them came from the general public. The patient was advised to stay at home and a visit to an emergency department was avoided in 6,417 cases. *Conclusions:* Based on our results, we can conclude that the main objectives of the collaboration were accomplished. Cost-savings can be estimated as important since direct access to PCC reduced the unnecessary use of emergency health care resources. Besides we have provided timely and appropriate treatment recommendations in poisoning episodes and mitigated serious health consequences such as inadequate treatment. The close contact with the manufacturers has helped us in toxicological emergencies and toxic surveillance.

171. Inquiries Concerning Poisonings in Dogs During 2001–2003

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Objective: Animal-related inquiries received by Finnish Poison Information Centre have been increasing in the recent years more rapidly than the total number of calls. Dogs have been leading species involved in the calls. The objective of the study was to analyse the calls related to dog poisonings. The aim of the study was to investigate which were the most common substances causing poisonings in dogs. *Method:* Since June 2000 all calls to the Finnish Poison Information Centre are recorded on a computer database. A retrospective study of calls related to dog poisonings during the years 2001–2003 was performed employing the current database. *Results:* The total number of calls concerning animals in the 3 years was 6,859, and 5,557 (81%) involved dogs. From these 4 999 were related to suspected or confirmed poisonings and 558 were general inquiries. The majority of the poisonings (56%) could be grouped under: human medicinal products (n=1,091), plants (n=912) and ''miscellaneous'' substances (n=809). The ten most common substances in dog poisoning inquiries were rodenticides (n=272), insecticides (n=132), detergents (n=130), chocolate (n=122), ibuprofen (n=115), chewing gum (n=105), tobacco (n=103), clinical thermometer (n=102), batteries (n=100) and blue-green algae (n=93). *Conclusion:* The anticoagulant rodenticides continue to pose a considerable potential risk for pets, especially dogs, which often consume them quite large amounts. Since modern rodenticides are usually long-acting, K-vitamin therapy should be given for several days (14–30 days) after exposure. In addition to the widely known toxic substances, also chocolate and xylitol-containing chewing gum are particularly toxic for dogs. Ibuprofen tablets can cause stomach ulcers in dogs even in small doses. Owner education is crucial in attempting reduce pet poisonings: All animals should be supervised outdoors. Drugs should be used only for the specified species and all harmful substances, including over-the-counter drugs, should be kept out of the reach of all pets.

172. The Use of National Poisons Information Services by Ambulance Personnel

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Objective: To investigate use of a poisons telephone enquiry service and Internet clinical toxicology database by ambulance personnel. *Background:* The major users of TOXBASE, the UK National Poisons Information Service (NPIS) Internet poisons database, are hospital accident and emergency departments (A&E). Recently a number of ambulance services have registered

but most access it only occasionally. *Method:* Postal questionnaires were sent to 90 registered ambulance service users of TOXBASE asking them for data concerning their service, computerisation, and use and satisfaction with the NPIS telephone enquiry service and TOXBASE. For some questions a scale of 1–6 was used with 6 being used to express greatest satisfaction. Medians and 95% confidence intervals (CI) were calculated. *Results:* Ambulance users of TOXBASE logged on to the database 1–379 times (median 8) in the first 9 months of 2004. 36 replies were received (40.0%) with one of the replies covering several centres. Replies came from a combination of ambulance service units—ambulance station (16), ambulance control (11), emergency planning (7), clinical governance (3), others (4). Centres had 1–300 staff consisting of paramedics, technicians, call handlers, supervisors and managers. 30 (83.3%) had computers in ambulance stations; 26 (72.2%) in ambulance control; 26 (72.2%) in training departments; only five had Internet access from ambulances. 15 sometimes used NPIS telephone services (for overdoses, incident support and chemical incidents). Other sources of poisons information included local A&E departments (8), computer databases (4), Internet (3), government agencies (2), textbooks (2), the British National Formulary (2) and the fire service (2). Of those who never used TOXBASE one preferred to telephone NPIS for advice and three to contact A&E. One centre used TOXBASE frequently: eight once a week, two once a month and the remainder less frequently. On a score of 1–6 TOXBASE was the preferred source of poisons information: median score 5 (95% CI 4–6); contacting A&E 4 (95% CI 2–4); telephoning NPIS 4 (95% CI 2–5). 18 centres used TOXBASE for education and clinical management, five for education and five for clinical management only. 16 used TOXBASE for advising at incident scenes, personal study (15), formal training (13), advising staff (13). TOXBASE was used for chemical incidents (17), emergency planning (12), deciding whether a patient should go to A&E (8), whether a patient needed charcoal (3), advice if a patient refused to go to hospital (1), effects of drugs (1). TOXBASE was generally considered easy to access: median score 5 (95% CI 5–6); with sufficient information 5 (95% CI 5–5) and overall satisfaction scored median 5 (95% CI 5–6). *Conclusions:* Ambulance services prefer to use TOXBASE or contact A&E for poisons information rather than telephoning NPIS services. TOXBASE is used for chemical incidents, training and emergency planning.

173. Consensus on Carbon Monoxide Treatment and HBO Therapy Among Us Poison Centers—Responses to a Survey

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Background: Carbon Monoxide (CO) toxicity is a common poisoning responsible for significant morbidity and mortality, yet there is no established consensus on the use of hyperbaric oxygen (HBO) therapy among US poison centers. We were interested in evaluating the responses from medical directors to a survey about CO poisoning and HBO therapy. *Methods:* A seven-question survey based on a hypothetical, single patient CO scenario was distributed twice through the medical directors' internet mailing list. The questions were a combination of YES/NO and multiple-choice responses. Questions focused on HBO recommendations (number and timing of dives), identifying cardiac ischemia, and the use of HBO in an asymptomatic patient. We calculated the frequencies of responses. *Results:* Twenty-five out of 62 (40.3%) poison centers' medical directors responded. One hundred seventy out of 175 questions (97%) were answered. Positive response rates ranged from zero to 64%. No consensus was reached regarding the use of HBO for the asymptomatic, non-pregnant patient based upon CO level. *Conclusion:* There was no consensus among US poison center medical directors with regard to general recommendations for the treatment of CO poisoning or the use of HBO. The use of HBO therapy for CO toxicity should be considered for AACT/EAPCCT consensus-based guidelines.

174. QTc Interval Prolongation Associated with Escitalopram Overdose

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Objective: Case series and reports have demonstrated that citalopram overdose can result in QTc prolongation, due to its didesmethylcitalopram (DDCT) metabolite. In overdose, the prolonged half-lives of citalopram and its metabolite may be responsible for delayed cardiac effects more than 12 hours post-ingestion. Escitalopram is the S-enantiomer of citalopram, and is

responsible for citalopram's therapeutic activity. It is metabolized to the S-enantiomer of DDCT. QTc prolongation has not been previously reported with escitalopram use. We report the first case of an escitalopram overdose associated with QTc interval prolongation. *Case Report:* A 52 year-old woman with schizoaffective disorder presented to the emergency department (ED) 72 hours after a self-reported overdose of 71 tablets of her escitalopram and 29 tablets of her aripiprazole. The patient was on no other medications and she did not know the dose per tablet. She was asymptomatic with an oral temperature of 36.8 degrees C, heart rate of 72/min, respiratory rate of 14/min, and blood pressure of 106/64 mm Hg. Her physical examination was unremarkable. An acetaminophen level was negative, and electrolytes and liver function tests were normal. A screening electrocardiogram (ECG) revealed a prolonged QTc of 484 msec. Her QTc was 403 msec on an ECG taken 10 months prior. The patient was observed in the ED and remained asymptomatic. A repeat ECG 13 hours later showed resolution of the ECG abnormality, with a QTc of 411 msec. Serum aripiprazole level was 280 ng/mL. Steady state aripiprazole levels in patients taking 30 mg/day range from 126 ng/mL to 585 ng/mL. Serum escitalopram level was 200 ng/mL. A steady state peak plasma escitalopram level in patients taking 30 mg/day is 64 ng/mL. *Conclusion:* This report demonstrates that QTc interval prolongation may occur in the setting of escitalopram overdose. The QTc interval prolongation was unlikely to be due to aripiprazole since the patient had a therapeutic or sub-therapeutic drug level. Patients presenting with an escitalopram overdose should be monitored for QTc interval prolongation.

175. Recurrent Torsades Des Pointes After Abrupt Self-Escalation of Dose in a Chronic Methadone Patient

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Objective: Torsades des pointes (TdP) and QTc prolongation are loosely associated with very-high dose methadone. Levacetylmethadol (LAAM), a methadone derivative, was withdrawn from the market for its association TdP. We clearly document QTc prolongation and TdP associated with a large and abrupt increase in methadone dose. *Case Report:* A 34 year-old woman with chronic back pain presented to the ED with numerous ''jerking'' episodes associated with a ''dazed'' stare. These witnessed episodes lasted seconds and were not associated with loss of consciousness or loss of postural tone. Her physical exam was unremarkable; P 90 beats/min, BP 110/70 mm/hg, RR 16, afebrile. She reported no prodromal symptoms or previous similar events and no recent trauma. She had no past medical history of seizures or syncope and no family history of sudden cardiac death. She denied taking any new prescription drugs or herbals, but admits to smoking marijuana occasionally. Her medications included; methadone 60 mg po bid, baclofen 5 mg po tid and oxycodone 5 mg po prn. All the doses were reported to be stable doses for ''months''. Her elecrocardiogram showed a normal sinus rhythm at 87 beats/min with a QTc of 523 ms. Blood laboratory analysis was unremarkable, including serum electrolytes. Urine toxicology screen for common drugs of abuse was positive only for marijuana. While on a cardiac monitor she experienced another episode and was noted to have TdP. She was electrically cardioverted and treated with intravenous lidocaine. Several minutes later TdP recurred and rapidly degenerated into ventricular fibrillation. She was defibrillated and intravenous magnesium sulfate was administered. She was transferred to the CCU on a lidocaine infusion. All other medications were held. She remained on a lidocaine infusion and had a single self-terminating episode of TdP approximately 30 hours later (QTc was 420 ms at that time). At 72 hours post ingestion her QTc had normalized to 380 ms. She had a negative EPS and a normal EF on echocardiography. No TdP occurred and she was discharged in good health approximately one week later with an implantable cardioverter defibrillator. She later admitted to self-medicating with an additional two 80 mg methadone doses in the past 24 hours for worse pain. *Conclusion:* Very-high dose methadone is associated with TdP. This patient developed greater than ten episodes of TdP associated with a new prolonged QTc after abruptly and significantly increasing her methadone dose. The QTc prolongation and arrhythmias resolved upon discontinuation of methadone. It may be prudent to evaluate screening and follow-up electrocardiograms in patients on high-dose methadone.

176. Long QT Syndrome Induced by Oxatomide Overdose in Children

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Objective: To describe cardiotoxic effects in pediatric patients with oxatomide overdose. *Methods:* All cases of pediatric oxatomide overdose referred to a Poison Center over a 4-year period were analyzed. For each patient 1) overdose circumstances,

2) amount ingested, 3) concomitant therapy, 4) symptoms, 5) serum oxatomide levels performed with HPLC, and 6) QTc interval were evaluated. *Results:* We examined 12 patients (mean age: 42.4 months, range: 21 days-14 years) admitted to hospital for oxatomide overdose. Ten subjects had taken the drug in a single dose ranging from 1.6 to 30 mg/kg; two other patients had been repeatedly treated with oxatomide at doses higher than those recommended in children. Serum oxatomide levels measured in 8 patients were 105–1300 ng/ml (therapeutic range: 20–40 ng/ml). A total of 5 children (5/12, 41.6%) developed QTc prolongation (447–639 msec). In this group, 2 patients had ingested a single high dose of oxatomide and 1 patient had repeated supratherapeutic dosing. In one patient showing very high serum concentrations (400 ng/ml) despite moderate drug overdosage (3 mg/kg), oxatomide had been coadministered with erythromycin. The maximum QT prolongation was found in a 3-week old patient following ingestion of 6.9 mg/kg oxatomide. Four patients in the group with drug-induced ECG abnormalities showed normal QTc at discharge. *Conclusion:* Overdose of 2nd generation antihistamines has often been associated with prolongation of the QTc interval. In this respect, no data are available on oxatomide, an agent which is largely used in Italy at the recommended dosage of 0.5 mg/kg bis in die. Previous reports of human cases of oxatomide overdose in the peer-review medical literature are lacking. A Medline search documented only extrapyramidal effects at near-to-therapeutic doses in children (1). In experimental studies performed in conscious dogs, it has been shown that oxatomide does not induce QT prolongation as a single agent at the dose of 30 mg/kg (2). Our observations indicate that oxatomide poisoning can prolong QT interval in children at lower doses. In the patients reported here, a clear proportion between ingested dose and oxatomide serum levels was not established: this can be related to the approximate nature of the ingested dose, to metabolic interactions, and/or to genetic susceptibility due to polymorphism in genes encoding for myocardial potassium channels, as already documented in an adult patient (3). *References:* 1. Casteels-Van Daele M, Eggermont E, Casaer P, et al. Acute dystonic reactions and long-lasting impaired consciousness associated with oxatomide in children. *Lancet* 1986; 1(8491):1204–1205. 2. Iwamoto K, Ikeda J, Nito M, et al. Effect of oxatomide, an antiallergic agent, on QT interval in dogs. *Arzneim Forsch Drug* Res 2001; 51:971–978. 3. Sesti F, Abbott GW, Wei J, et al. A common polymorphysm associated with antibiotic-induced cardiac arrhythmia. *PNAS* 2000; 97:10613–10618.

177. Electrocardiogram Abnormalities Encountered in Poisoned Patients

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Introduction: Poisoned patients frequently demonstrate abnormality on the 12-lead electrocardiogram (ECG), including both rhythm and morphologic issues. *Objective:* The following study was undertaken to consider the range of ECG abnormality noted in poisoned patients. *Methods:* All patients evaluated by a University Clinical Toxicology Consultation Service over a year's time span were entered into the study. All poisoned patients with ECGs performed within 6 hours of toxin exposure were entered into the study group and were used for the data analysis. Each ECG was reviewed for both rhythm and morphological diagnosis by 5 clinicians (4 emergency physicians and 1 cardiologist), with final consensus of findings based on majority diagnosis. ECG interval durations were also noted using the ECG machine-provided measurements. *Results:* A total of 624 patients were encountered over a year's time; 277 (44%) of patients (mean age 35.4 years with a range of 0.8 to 84 years) underwent ECG evaluation and were used for data analysis. A total of 88 (32%) of patients had a normal ECG. Of those with abnormal ECGs (189, 68%), 117 (62%) had rhythm abnormality while 72 (38%) had morphologic abnormality. Rhythm disturbances included sinus tachycardia (88), other atrial tachycardias (7), sinus bradycardia (12), atrial-ventricular block (8), and nodal bradycardia (5). Morphological abnormality included the following: PR interval prolongation (13), QRS complex widening (34), QT interval prolongation (33), ST segment abnormality (10 elevated, 26 depressed), T wave abnormality (80 inverted, 3 prominent), and abnormal QRS configuration (36 with R-wave in lead aVR and S wave in lead 1). *Conclusion:* ECG abnormality is frequently encountered in poisoned patients, including both rhythm disorders as well as morphological anomaly.

178. Brugada Sign in an Acute Diphenhydramine Intoxication

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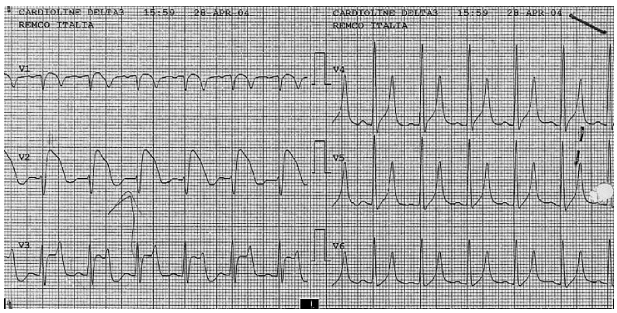

FIG. 1.

Objective: We report the case of a patient admitted in deep coma after ingestion of a toxic dose of diphenhydramine in whom a Brugada sign was detected in the electrocardiogram. *Case Report:* A 39-year-old man was discovered in his home in a deep coma, with indications of attempted suicide by ingestion of diphenhydramine and ethanol. On arrival at the emergency unit, the Glasgow Coma Score was 3 and the patient had hypotension and mydriatic pupils. The ECG showed an elevation of 9 mm in the ST segment in leads v2–v3, compatible with a Brugada sign (Fig. 1). Tests showed metabolic acidosis and hyperkalemia. Blood ethanol level was 1.3 g/L. Toxic screening by HPLC analysis confirmed the presence of diphenhydramine in the urine. Initial treatment consisted of intubation and mechanical ventilation. A gastric lavage was carried out and activated charcoal administered. Intravenous plasma expanders and sodium bicarbonate were administered. The ECG progressively normalized, the patient recovered consciousness and mechanical ventilation was discontinued at 24 hours. With the standardized ECG, a flecainide provocation test was carried out which was negative. The patient confirmed voluntary ingestion of diphenhydramine and was discharged without sequelae 7 days after admission. *Conclusion:* Diphenhydramine intoxication may cause electrocardiographic anomalies in the form of a Brugada sign, which in other types of intoxications has been associated with a worse prognosis. 24-hour ECG monitoring is necessary in severe diphenhydramine intoxications. *References:* Littmann L, et al. Brugada syndrome and ''Brugada sign.'' Clinical spectrum with a guide for the clinician. *Am Heart J* 2003; 145:768–778. Zareba W, et al. Electrocardiographic findings in patients with diphenhydramine overdose. *Am J Cardiol* 1997; 80:1168–1173. Sharma NA, et al. Diphenhydramine-induced wide complex dysrhythmia responds to treatment with sodium bicarbonate. *Am J Emerg Med* 2003; 21:212–215.

179. Acute Carbamazepine Toxicity Associated with a Widened QRS Interval Treated with Intravenous Sodium Bicarbonate

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Objective: Acute carbamazepine (CBZ) toxicity is commonly associated with various clinical manifestations including sedation, ataxia, nystagmus, and seizures. Although significant cardiac toxicity is uncommon, sodium channel blockade and subsequent QRS interval prolongation are reported. We present a case of a child with a widened QRS interval following an acute CBZ overdose that was successfully treated with intravenous sodium bicarbonate (IVSB). *Case Report:* A 3 year-old female, weight 20 kg, with no significant past medical history, presented to the Emergency Department (ED) with altered mental status. She had ingested an unknown amount of her older sister's CBZ. Her initial vital signs were: pulse: 120 beats per minute; blood pressure: 104/58 mm Hg; respiratory rate: 22 breaths per minute; temperature: 35.9°C (96.7°F); oxygen saturation of 98%. On physical examination, her pupils were approximately 3 mm bilaterally and minimally responsive, with no nystagmus or dysconjugate gaze. Her skin and mucous membranes were warm and moist. On neurologic examination, she was obtunded and unresponsive to painful stimuli. The patient was intubated by rapid sequence intubation. After intubation she was sedated with periodic doses of intravenous lorazepam. Her initial electrocardiogram (ECG) demonstrated a sinus rhythm, rate of 121 beats per minute and a QRS interval duration of 92 msec. Via a nasogastric tube, the patient was administered 20 g of activated charcoal and 21 g of sorbitol. A second ECG performed one hour later revealed a QRS interval duration of 102 msec. The patient was given a bolus of (1 mEq/kg) IVSB, and an ECG repeated 1 minute later demonstrated a narrowing of the QRS interval to 84 msec. Due to the therapeutic response of the IVSB the patient was started on a continuous infusion of IVSB at 90 mL/hour. The initial and peak

serum CBZ level was 24.5 μg/L. The patient was admitted to the Pediatric Intensive Care Unit (PICU). She received the infusion of IVSB for a total of approximately 11 hours. Daily ECGs showed no further widening of the QRS complex and a stable QRS interval duration of approximately 80 msec. She remained in the PICU for 48 hours and she was always hemodynamically stable. She was discharged home from the hospital after 4 days with no significant sequelae. *Conclusion:* To our knowledge, this is the first reported case of a patient with acute CBZ toxicity associated with a widened QRS interval duration that was successfully treated with IVSB. In addition to other toxicologic etiologies, narrowing of the QRS complex following IVSB administration should prompt consideration of acute CBZ toxicity.

180. Digoxin Toxicity from Intentional Intravenous Injection: A Case Report Treated with Digoxin-Specific Antibody Fragments

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Objective: We report an unusual case of intentional poisoning by digoxin intravenous (IV) injection, treated with digoxin-specific antibody fragments (Fab). *Case Report:* A 52-year-old, 73 kg general practitioner, with a history of depression, presented to the hospital 2 hours after self injecting methyl-digoxin 6 mg (Lanitop® 0.2 mg/vial, 30 vials) in a suicide attempt. He complained of vomiting. Examination of an antecubital puncture mark revealed recent IV injection. His blood pressure was 125/80 mm Hg. The electrocardiogram showed sinus arrest and supraventricular escape rhythm with a rate of 70 beats/min. Digoxin serum level was 13.5 ng/mL (therapeutic range 0.6–2). At this time serum potassium was not measured. Shortly after Fab administration (456 mg in order to achieve equimolar neutralization), electrocardiogram demonstrated sinus rhythm with a borderline PR interval (0.20 seconds) and potassium was 5.5 mEq/L. During the following 45 hours, the patient presented a varying degree of vomiting, hallucinations and visual disturbances. Rhythm strip performed at 16 hours post injection showed sinus rhythm with first degree atrioventricular block (PR 0.22); at 28 hours PR interval increased (0.24) and inverted T waves appeared. At 40 hours post injection, cardiac toxicity increased resulting in an alternating second degree atrioventricular block, appearing during Valsalva manoeuvres, and atrioventricular dissociation without hemodynamic effects. In the next hour, while the administration of a second dose of Fab was considered, electrocardiographic abnormalities spontaneously improved. Two hours later, an ectopic atrial rhythm with normal PR interval and reduced repolarization abnormalities appeared. A further dose of Fab was never given. Renal function remained normal during the clinical course. The patient was discharged on day 6 with a normal electrocardiogram. *Conclusion:* The observed clinical course could be explained only by a rebound in free digoxin levels, since no delayed absorption can be advocated. Unfortunately, assay-related problems hampered free digoxin monitoring after Fab use. Electrocardiographic abnormalities were the cornerstone of this case of poisoning: electrocardiogram revealed immediate and useful information to direct patient care, confirming that continuous clinical and electrocardiographic monitoring in an intensive care setting is mandatory in digitalis poisoning. *Reference:* Taboulet P, Baud FJ, Bismuth Ch. Clinical features and management of digitalis poisoning—rationale for immunotherapy. *J Toxicol Clin Toxicol* 1993; 31(2):247–260.

181. Falsely Elevated Serum Digitoxin Concentrations Measured by Immunoassay Using Murine Antibodies in a Clinical Asymptomatic Patient

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Objective: The low specificity of immunoassays compared to other analytical methods (HPLC, LC-MS) used for the routine Therapeutic Drug Monitoring of patients undergoing digitoxin therapy can lead to some pitfalls. We report about a highly elevated digitoxin serum concentration measured by an immunoassay method using murine antibodies (Advia, Bayer) in a clinical asymptomatic patient. *Case Report:* A 73 years old patient stayed in hospital for treatment after a threefold coronary bypass operation. The digitoxin serum concentration was 83.6 nmol/l although the patient had received his last digitoxin medication in a therapeutic dose 3 weeks ago. In ECG a known normofrequent absolute arrhythmia was observed. Bloodpressure was 120/70 mm

Hg and no clinical signs of digitoxin toxicity were seen in the patient during his stay in hospital over 3 weeks. After remeasurement of the same serum samples by another immunoassay not using murine antibodies (Dimension, Behring) the digitoxin serum concentration was 6.06 and 7.2 nmol/l, respectively. As possible explanation for this phenomenon of falsely elevated digitoxin serum levels the generation of autoantibodies against murine antibodies in the patient was discussed because he had received murine antibodies (Abiximab) to prevent aggregation of thrombocytes in 1998. However, other substances (endogenous and nutritional) causing crossreactivity have to be considered, as well. Being alert of this phenomen we observed at least four other cases during 2000 and 2004 with discrepance between high elvated digitoxin serum concentration and a lack of clinical symptoms. In literature this observation has been made, as well (Biddle et al., 2000). In these cases with discrepance between high elevated digitoxin serum concentration and lack of clinical symptoms we recommend to treat the patient according to his clinical symptoms and to determine the digitoxin serum concentration by a specific method (HPLC or LC-MS). *Conclusion:* Because of low specificity of immunoassays falsely elevated serum digitoxin concentrations can be observed in asymptomatic patients. In these cases a remeasurement by a specific method (HPLC, LC-MS) and a treatment according to the symptoms is recommended. *Reference:* Biddle DA, Datta P, Wells A, et al. Falsely elevated serum digitoxin concentrations due to cross-reactivity of water-extractable digitoxin-like immunoreactivity of Chinese medicine Chan SU: elimination of interference by use of a chemiluminescent assay. *Clin Chim Acta* 2000; 300:151–158.

182. Cardiac Arrest Following an Intravenous Pentamidine Overdose

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Objective: To report cardiac arrest following an intravenous pentamidine overdose in an infant. *Case Report:* A 6-month-old female was admitted to the hospital secondary to severe combined immunodeficiency syndrome. In preparation for a stem cell transplant, pentamidine prophylaxis therapy for *Pneumocystis carinii* pneumonia (PCP) was instigated. Within 5 minutes of the initiation of the third dose of a three-day load of intravenous pentamidine, the infant became cyanotic, followed by apnea and absence of palpable femoral pulses. CPR was initiated and the infusion of pentamidine was stopped immediately. Femoral pulses became palpable and compressions were discontinued in approximately one minute. The infant did not require endotracheal intubation but was transferred to the pediatric intensive care unit for continuous cardiopulmonary monitoring. She remained stable overnight and throughout the next day. Her subsequent blood pressure, electrocardiogram, glucose, serum chemistries and pancreatic enzymes remained normal. Upon analysis of the pentamidine syringe and preparation records, the pentamidine solution had been mixed incorrectly. The patient received approximately 75 mg while the intended dose was 4 mg/kg (26 mg). Furthermore, the pentamidine loading dose had been ordered twice, two weeks apart, instead of the usual regimen consisting of one load of 4 mg/kg/day for 3 days, followed by a single 4 mg/kg dose every two weeks. *Conclusion:* An adverse effect rate of up to 50% has been observed in patients receiving intravenous pentamidine. This antibiotic has the following toxicities when given in therapeutic doses: hypotension, hepatic dysfunction, hypoglycemia, nephrotoxicity, anaphylaxis, ventricular arrhythmias and sudden death. Particularly concerning are reports of prolonged QT interval and torsades de pointes (TdP), even in patients receiving therapeutic doses of pentamidine for the treatment of PCP (1). Multiple drug classes have been implicated in prolonging the QT interval with subsequent TdP, including antipsychotics, antiarrhythmics and certain antimicrobial agents (2); these medications may block the human ether-à-go-go-related gene (hERG)-encoded channels, inhibiting release of potassium from the myocytes. Most cases of TdP have been reported in patients with additional risk factors such as multiple drug regimens, genetic predisposition, underlying organ dysfunction or electrolyte imbalance. This case report emphasizes that both the rapid infusion of intravenous pentamidine isethionate, in combination with an incorrect dosing regimen, can cause TdP with subsequent cardiac arrest and should be avoided. *References:* 1. Miller HC. Cardiac arrest after intravenous pentamidine in an infant. *Pediatr Infect Dis J* 1993; 12(8):694–696. 2. Owens RC, Jr. QT prolongation with antimicrobial agents: understanding the significance. *Drugs* 2004; 64(10):1091–1124.

183. Comparative Evaluation of Wide QRS and R Changes in AVR Lead in Predicting of the Severe Complications of Tricyclic Antidepressant Poisoning

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Introduction: Trcyclic antidepressants (TCAS) Poisoning is the most common poisoning in the Poisoning Emergency Department of Noor Hospital, Isfahan, Iran. With considering of the severe cardiovascular and central nervous system complications associated with TCAs toxicity and great number of TCA poisoned patients in Noor Hospital, precise investigation was done. The objective of this study was to compare QRS interval duration with $R_{aVR} \geq 3$ mm and $R/S_{aVR} \geq 0.7$ in predicting: serious complications of acute TCA toxicity. *Methods and Materials:* This study was descriptive—analytic and prospective cohort. TCA poisoned patients (155) were evaluated in the Emergency Department of Noor Hospital, Isfahan, Iran from March 2002 to March 2003. On admission time, ECG and ABG were done. Data were analyzed by SPSS Software, using t—students and chi-square tests. *Results:* The results showed that most patients were 11–30 year olds (78.1%); women (60%) and the 55% of the patients were married (55%). The ECG results showed that $R_{aVR} \geq 3$ mm, $R/S_{aVR} \geq 0.7$, QRS ≥ 0.1(s), QT > 0.48(s). Right axis deviation and arrhythmia were 5.2%, 12.9%, 37.4%, 8.38%, 12.4% and 4.5% respectively. The incidence of non-cardiac complications were as follows: Loss of consciousness (85.5%), Acidosis (65%), Mucus dryness (55.6%) and Mydriasis (25.2%). There was a significant relationship between widening QRS with arrhythmia; $R_{aVR} \geq 3$ mm with tachycardia and delirium; and $R/S_{aVR} \geq 0.7$ with delirium, seizure, tachycardia, hypotension and arrhythmia. There was also a significant relationship between Prolonged QT with seizure and agitation. A rightward deviation of the vector of the QRS Complex between 130° and 270° was related to arrhythmia. QRS interval duration (61.5%–85.7%) was found to be a more sensitive indicator of toxicity than the $R/S_{aVR} \geq 0.7$ (27.1%–30.7%) and $R_{aVR} > 3$ mm (7.6%–14.2%). The positive Productive Values (PPV) of ECG parameters for TCA toxicity for $R/S_{aVR} \geq 0.7$ (20%) was more than $R_{aVR} \geq 3$ mm (12.5%) and widening QRS (10.3%). *Conclusion:* Specific ECG parameters such as R/SaVR, QRS interval duration and height of the R wave in lead aVR can be useful parameters in assessing and predicting cardiac and CNS complication of TCA toxicity. *References:* 1. Shannon MW, Haddad LM. The emergenecy management of poisoning. In: Haddad LM, linical management of poisoning and drug overdoes. 3rd ed., Phladelphia: Saunders Company, 1998: 2–3. 2. Pentel PR, Keyler DE, Haddad LM. Tricyclic antidepressants and selective serotonin reuptake inhibtors. In: Haddad LM. Cilinical management of poisoning and drug overdose. 3rd ed., Philadelphia: Saunders Company, 1998: 437–451. 3. Ellenhorn MJ. Ellenhorn's medicial toxicology diagnosis and treatment of human poisoning, 2nd ed., Baltimore: Williams & Wilkins Company, 1997: 624–639. 4. William ZP, Leo EH. Antidepressant agents. In: Katzung BG, Basic and clinical pharmacology, 7th ed., Norwalk: Appleton & Lange Company, 1998: 483–495. 5. Boehnert MT, Lovejoy FH. Value of the QRS duration versus the serum drug level in prediciting seizures and venticular arrhythmias after an acute overdoes of tricyclic antidepressant. *N Engl J Med* 1985; ??:373–474. 6. Niemann JT, Bessen HA, Rothstein RJ, Lake MM. Electrocardiographic criteria for tricyclic antidepressant cardiotoxicity. *Am J Cardiol* 1986; 57:1154–1159. 7. Lieblet EL, Francis PD, Woolf AD: ECG lead aVR versus QRS interval in predicting seizures and arrhythmias in acute tricrcylic antidepressant toxicty. *Ann Emery Med* 1995; 26:195–201. 8. Caravati EM, Bossart DJ. Demographic and electrocardiographic factors associated with severe tricyclic antidepressant toxicity. *J Toxciol Clin Toxicol* 1991; 29:31–43.

184. Adverse Effects of Barium Esophagram Used for the Evaluation of a Caustic Ingestion

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Objective: Endoscopy (EGD) is a commonly recommended diagnostic procedure to evaluate the extent of gastrointestinal (GI) injury from caustic ingestions. Barium esophogram (BE) is generally used for follow-up examinations of the GI tract. We report the case of a patient with a caustic ingestion managed with a BE instead of EGD who developed significant complications secondary to the procedure. *Case Report:* A 59-year-old gentleman presented to the emergency department (ED) after the ingestion of an unknown quantity of an alkaline drain cleaner. He complained of bloody saliva and mouth and throat pain. On physical examination his vital signs were: blood pressure: 136/72 mm Hg; pulse: 85/min; respirations: 23/min; temperature: 37.2°C (98.9°F); and oxygen saturation of 98%. He had a normal mental status. The mucosa of the lips and tongue were erythematous with ulcerations on the soft palate, hard palate, and buccal mucosa. The patient immediately received intravenous dexamethasone and famotidine. Fiberoptic laryngoscopy revealed ''beefy red'' erythema throughout the oral cavity with areas of granulation tissue on the tongue. The glottic airway was patent but there was supraglottic and posterior cricoid erythema and edema. The gastroenterology service recommended conservative management and EGD at 24 hours. Initial chest radiography showed no signs of perforation. A BE was recommended by the cardiothoracic surgery service which was initially reported as no signs of perforation; a possible distal stricture of the esophagus; atelectasis/collapse of the right lower lobe; and tracheal column displaced to the right side. The patient was admitted to the Surgical Intensive Care Unit. Three hours later the patient developed respiratory distress and he was endotracheally intubated. Tube thoracostomy was performed on the right lung for a presumed

right-sided pneumothorax. A CT scan of the chest showed dense consolidations of contrast in the upper and lower lobes of the right lung consistent with aspiration of barium from the BE. Throughout his hospital stay, he required several operative procedures including a tracheostomy on hospital day (HD) 4 and two laparotomies to remove both a necrotic stomach on HD 11 and the proximal jejunum on HD 19. The patient was discharged to a rehabilitation facility on HD 82. *Conclusion:* Performance of a BE following an acute caustic ingestion resulted in aspiration of barium and subsequent prolonged intubation and ventilatory support in this patient. While it is unclear whether performance of EGD would have altered patient outcome, it may have minimized the respiratory complications. This case supports the lack of utility and potential harm of BE in acute caustic ingestions.

185. Multidose Activated Charcoal and Albumin Dialysis (MARS) for Enhanced Elimination in a Case of Prolonged Coma Due to Clorazepate Potassium

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Background: Multidose activated charcoal (MDAC) is the most used technique to enhance elimination of exogenous substances in cases of prolonged courses of poisoning. Enhanced elimination techniques are not routinely used in benzodiazepine poisoning because of its short duration and the availability of a specific antidote, flumazenil. The Molecular Adsorbent Recirculating System (MARS) is a liver support system based on an albumin dialysis, recently developed to bridge liver failure until transplantation or recovery. This system could be an alternative elimination method for long-lasting benzodiazepines if MDAC and flumazenil fail. *Case Report:* A 82-year-old man was found at home in coma. On admission GCS score was 6, and he was intubated for airway protection. Emergency CT revealed no intracranial lesions. Temperature was 38.7°C, blood pressure 145/60 mm Hg and heart rate was 85/min with no other relevant findings. Urine toxicology screening revealed nordazepam and oxazepam. Serum concentrations were 9.96 μmol/L for nordazepam, the active metabilite of clorazepate, and 0.17 μmol/L for oxazepam, its subsequent metabolite. Treatment was supportive. On day 4, still comatose, he did not respond to 0.5 mg flumazenil iv. Then MDAC (50 g every 4 hours) was started because of prolonged coma with GCS 3. The plasma elimination half-life of nordazepam, based on daily plasma concentration measurements, was 192 hours before MDAC was started, and 144 hours during the three following days. On days 11 and 12 a trial to accelerate drug elimination with two 8-hour courses of MARS were performed to reduce his risk of ventilator associated pneumonia. The first MARS treatment reduced nordazepam plasma concentration (4.20 to 2.98 μmol/L) and oxazepam (0.12 to 0.80 μmol/L), while the second treatment did not alter nordazepam plasma concentration (2.62 μmol/L), and oxazepam concentration decreased only very little (0.7 to 0.5 μmol/L). The increased nordazepam and oxazepam concentrations within the albumin dialysate of the MARS could not explain the difference of efficacy between the two treatment courses. Moreover, plasma elimination half-life of nordazepam remained high (approx. 30 hours) after cessation of MARS therapy under reinstituted MDAC, suggesting a delayed charcoal effect or significant changes in nordazepam toxicokinetics. The patient regained consciousness on day 13 when plasma nordazepam concentrations reached 1 μmol/L, and was extubated on day 15. *Conclusions:* MDAC significantly reduced plasma elimination half-life of nordazepam in a patient with prolonged clorazepate-induced coma, whereas MARS did not contribute consistently to nordazepam elimination. These findings suggest that MDAC is the preferred elimination technique in prolonged nordazepam-induced coma.

186. Availability of Charcoal Hemoperfusion in Teaching Hospitals in Three US Cities

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Objective: To determine the availability of charcoal hemoperfusion (HP) in select US cities. *Methods:* A telephone survey of head dialysis nurses and nephrologists working in the inpatient hemodialysis units of teaching hospitals in Philadelphia, Chicago, and Los Angeles, was used to determine the capacity for emergency charcoal HP, the recent use of this technique, and the specific hardware used at each institution. *Results:* Responses showed geographic variablility. Both Los Angeles, as a

representitive Western US city, and Chicago in the mid-west each had several hospitals with the capability to perform HP. Hospitals familiar with the technique tended to report that HP was used only once every 2–3 years for toxicologic purposes. In, Philadelphia, a representative Eastern US city, however, none of 10 teaching hospitals had the capability to perform hemoperfusion on an emergency basis. *Conclusion:* The lack of emergency availability of charcoal hemoperfusion in a major population center of the U.S. was a surprise. Further research would be required to determine if this was due to regional differences in population and exposure patterns, or soley explained by varying regional practice styles. The lack of widespread availability should lead to a re-examination of the utility of the technique in the setting of newer, more efficient techniques for hemodialysis.

187. Is Digoxin Poisoning Improved by Insulin? A Case Report

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Objective: Digoxin antibodies are the treatment of choice for digoxin poisoning. Insulin-glucose has been proposed as an adjunctive therapy for severe calcium channel and beta blockers poisoning. We report a case of digoxin and insulin poisoning who did not develop life-threatening features despite the ingestion of a high dose of digoxin and high digoxin serum levels. *Case Report:* A 35-year-old woman ingested in a suicide attempt 17.5 mg digoxin, 3.4 g propranolol, 400 mg domperidon and 180 mg bromazepam. When the emergency medical unit arrived at home, 5 hours post ingestion, the patient was comatous (GCS 6) with vomitings. Blood pressure was 115/80 mm Hg and pulse rate was 40/min. The initial fingerstick glucose level was undetectable. After iv infusion of 6 g glucose the glycemia was 0.4 g/l. The patient was immediately intubated. ECG after 1 mg atropine showed a sinus rhythm of 71 c/min. On admission in the ICU (H 6), the patient was comatose (under sedation) and ventilated. Blood pressure was 120/80 mm Hg, pulse rate was 50/min. Other physical examinations were normal. ECG showed a 1st degree atrio-ventricular block. Other biomedical investigations, chest X-ray, blood gases, creatinine, electolytes (kalemia=3.6 mmol/l) were normal except a severe hypoglycemia of 0.04 g/L. Over the following 24 hours, infusion of 300 g glucose was necessary in order to obtain an euglycemia. Blood pressure remained normal and cardiac rhythm ranged between 44 and 70 c/min without catecholamines or atropine. No biological abnormalities, especially no hyperkaliemia, were observed. The first degree a-v block disappeared spontaneously at H 10. Serum digoxin levels (ng/ml) were respectively: 9.2 (H6), 8.5 (H11), 7.7 (H16) 2.7 (H40) and 1.5 (H64). Propranolol serum level was 706 ng/ml (H6). The patient was extubated on day 3 and transferred in a medical unit on day 4. When the patient became conscious, she confirmed that she had self-injected 50 units of regular insulin (treatment of her father). *Conclusion:* In acute digoxin poisoning, the indication of digoxin antibodies is based on the occurrence of severe dysrhythmias, hemodynamic failure and hyperkalemia. In acute poisonings, a dose ingested higher than 10 mg digoxin and serum levels higher than 8 ng/ml are usually associated with life-threatening features. Our patient did not develop severe poisoning, especially no hyperkalemia, despite the ingestion of 17.5 mg digoxin, a digoxin serum level of 9.2 ng/ml and an associated ingestion of a beta-blocker. Insulin-glucose has been proposed for the treatment of some antiarrhythmic poisonings, especially calcium channel blockers. We raise the hypothesis that in our patient the associated poisoning with insulin may have had a protective effect on the toxicity of digoxin. References. 1. Dawson AH, Whyte I. *Br J Clin Pharmacol* 1999; 48:278–283. Yuan TH, et al. *J Toxicol Clin Toxicol* 1999; 37:463–474.

188. Comparison of the Scottish Early Warning Score and Poisons Severity Score in Assessing Illness Severity in the Poisoned Patient

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Objectives: The Poisons Severity Scale (PSS) was developed as a marker of illness severity in poisoned patients but requires retrospective analysis of the clinical condition of the patient. Early warning scores were developed to determine illness severity and identify patients at risk of clinical deterioration. They are based on simple ward observations. The Scottish Early Warning Score (SEWS) was recently introduced as an assessment tool but its value in the poisoned patient has never been studied. The aim of our study was to compare SEWS and PSS in a group of poisoned patients. *Methods:* PSS grades severity of poisoning as

0–4 ranging from no medical sequelae to death. SEWS is calculated by assigning weighted scores of 0–3 to each recording of pulse rate, systolic blood pressure, respiratory rate, temperature, oxygen saturation and conscious level assessment using AVPU. These values are summed to give a total SEWS score ranging from 0–18. Serial data from all patients admitted to the Toxicology unit of Edinburgh Royal Infirmary over a four month period were obtained from case records, anaesthetic and observation charts. Patients were followed from admission until discharge or death. *Results:* Data was collected on 253 patients. The severity of poisoning using PSS was 1 for 143 patients (56.5%), 2 for 65 patients (25.7%) and 3 for 29 patients (11.5%). 15 patients (5.9%) had no medical sequelae (0) and one patient died (4). There was no significant difference between PSS and class of drug ingested. The median SEWS score on admission was 1 (range 0–6). Patients who had used recreational drugs other than opiates had a significantly higher median admission SEWS score of 3 ($p<0.0001$). Median admission SEWS scores (with interquartile ranges) for patients with PSS of 0–4 were 0, 1 (0–2), 2 (1–3), 2 (1–4) and 1 respectively. Nine patients (3.6%) required intubation or admission to a critical care facility. These patients had a significantly higher PSS of 3 ($p<0.0001$) and higher admission SEWS score of 3 (IQR 1–6) ($p=0.002$) and maximum SEWS score of 4 (IQR 1–10) ($p=0.0001$). *Conclusion:* PSS was a good indicator of patients who required critical care admission but is of limited value in the routine management of patients. Patients with higher admission and maximum SEWS scores and were likely to need critical care intervention.

189. Bleeding Complications in Acetic Acid Poisoning Patients with Acute Renal Failure are Diminished with Citrate Hemodialysis

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Objective: Gasrointestitial (GI) bleeding in acetic acid poisoning is a life threatening complication which is aggravated by acute renal failure (ARF). Since it has been shown that citrate anticoagulation effectively prevents clotting in extracorporeal circuits we hypothesise that citrate anticoagulation might be advantageous in this patient group where major bleeding is a significant complication. (Flanigan et al., 1987). *Methods:* Complications in two groups patients with acetic acid poisoning and ARF have been evaluated. There were 100 patients (43 female, 67 male) in Group 1 and 100 consented patients (35 female and 65 male) in Group 2. Low dose heparin (7,58±0,5 ME units/min) and 4% sodium citrate (with concentration in circuit blood as 4,0±0,34 mmol/l) have been employed for blood anticoagulation for hemodialysis in 4,4±0,48 and 5,42±0,59 procedures per patient ($p>0,05$) in the Group 1 and the Group 2 respectively. Hemodialysis fluid was standard bicarbonate dialysate containing Na 138 mmol/l, K 2,5 mmol/l, Cl 112 mmol/l, HCO_3 28 mmol/l, Ca 1,75 mmol/l, Mg 0,75 mmol/l on Fresenius 4008S machine with 7HPS dialyser in each group. Dialysis duration was 4,0± 1,2 h, blood flow 250 ml/min, dialysate flow 500 ml/min. *Results:* Intradialytic complications in Group 1 and Group 2 (respectfully) were as follows: Intradialytic hypotension episodes occurred in 12,6% and 13,4%; hypertension in 3,2% and 3,9%; arrhythmias in 1,6% and 1,1%; rigors in 6,4% and 8,4%; extracorporeal circuit thrombosis 1,6% and 3,9% ($p=0,06$); citrate intoxication occurred in 0% and 6,7%; hematomas 9,5% and 1,1%; slight bleeding 6,4% and 0,6%; obvious bleeding with hypotension and discontinuing hemodialysis 7,9% and 1,1%; total bleeding complications 23,8% and 2,8%. Blood transfusion volume was 71,6±6,5 ml/kg in Group 1 and 34,8±5,9 ml/kg in Group 2 ($p<0,001$). And fresh frozen plasma transfusion volume was 52,4±3,3 ml/kg and 42,9±2,6 ml/kg ($p<0,05$) respectfully in Group 1 and Group 2. Blood transfusion volume was significantly increased by 103,1±72,9 ml; $p<0,02$ in Group 1. After citrate hemodialysis blood transfusion volume decreased by −38,8±72,5; $p>0,05$. There was significant differences in blood transfusion volume after hemodialysis among group 1 and 2 $p=0,02$. Mortality rate was 55,2% in Group 1 and 48,7% in Group 2. *Conclusion:* We conclude that anticoagulation with 4% sodium citrate for hemodialysis prevent bleeding aggravation in patients with acetic acid poisoning and may possibly decrease mortality. *Reference:* Flanigan MJ, Von Brecht J, Freeman RM, Lim VS. Reducing the hemorrhagic complications of hemodialysis: a controlled comparison of low-dose heparin and citrate anticoagulation. *Am J Kidney Dis* 1987; 9(2):147–153.

190. Oral Lead Poisoning Treated with DMSA and Surgery

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Objective: Evaluation of treatment options in a patient with lead retained in the intestines after oral lead poisoning. *Case Report:* A 32-year-old man was admitted to hospital complaining of abdominal pain, nausea and vomiting. Upon admission, he had normochromic anaemia with basophilic stippling (Hb 6.1 g/dL) and slightly abnormal liver enzyme values. Abdominal x-ray demonstrated two large areas of radiopaque small pellets in the intestines. Blood lead concentration was measured to 3.49 micromol/L. The patient claimed the lead poisoning to be a result of ingestion of game meat, which is highly unlikely considering the fact that the total amount was estimated to be more than 1200 pellets (about 120 g). Also several empty shotgun shells were found in his home. He was given DMSA treatment for three weeks, associated with a decrease in blood lead concentration to 3.01 micromol/L after one week, then the concentration rose again to 3.34 micromol/L, before it continued to decrease. Urinary lead excretion was not measured because of low compliance. During treatment with laxatives combined with manipulation of the patients position the amount of pellets in the intestines decreased, but about a half still remained in the caecum. Removal of pellets through colonoscopy was not effective, and laparotomy was therefore performed. All but one of the remaining lead shots were removed. Histology of the caecum showed mild inflammation. The patient was then given another treatment with DMSA with additional beneficial effects on the lead kinetics (S-lead now 2.14 micromol/L). He was discharged in good physical condition, but with neurological and neuropsychological sequels. *Conclusion:* DMSA treatment is associated with a decrease in blood lead concentrations, also when lead is still present in the intestines. Whether this decrease really represents an increased elimination of total body lead is unclear. Invasive procedures should be considered if toxic amounts of lead are retained in the body, and surgery may be indicated when a lot of small objects are present. In this situation endoscopic removal is difficult to perform and less effective. *References:* McKinney P. Acute elevation of blood lead levels within hours of ingestion of large quantities of lead shot. *J Toxicol Clin Toxicol* 2000; 38:435–440. McNutt TK, Chambers-Emerson JA, Dethlefsen M, Shah R. Bite the bullet: Lead poisoning after ingestion of 206 lead bullets. *Vet Hum Toxicol* 2001; 43:288–289.

191. Toxic Alcohol Exposures and Poisonings Treated with Fomepizole During a Two-Year Post-Marketing Surveillance in France

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Objectives: Toxic alcohol poisonings are rare. Fomepizole is the recommended antidote for the treatment of ethylene glycol (approval: 1999) and methanol poisonings (approval: 2001) in France. Our objectives were to describe patients treated with this antidote, to analyze fomepizole administration modalities, and to validate its safety (post-marketing surveillance). *Methods:* The very low treated patient number was a major issue to fulfil this follow-up. Consequently, we initiated this study with AGEPS, the marketing authorization holder and the unique supplier of fomepizole in France. In June 2002–June 2004, a questionnaire assessing fomepizole efficacy and safety was sent to every pharmacy ordering fomepizole. Pharmacists were systematically asked whether fomepizole supply concerned stock replacement or a new patient treatment. In this case, clinical and toxicological patient data were collected by the physicians in charge and sent to us. Results were expressed as % or median [10–90% percentiles]. Information on adverse drug reactions (ADRs) were extracted and analyzed. *Results:* Out of 179 hospitals, response rate to this survey was 46%. Fifty-three exposures or poisonings (39M/14F, age: 47 years [28–55], 5 children) corresponding to an incidence of 27 cases per year were reported: 31/53 to ethylene glycol and 18/53 to methanol, whereas 6/53 remained undetermined. Intoxication resulted from multidrug ingestion (24/53): ethanol (14/53), anxiolytics (7/53), and acetone (1/53). Among the patients who received fomepizole, 20/31 were really intoxicated with ethylene glycol (pH 7.16 [6.82–7.43], anion gap 31 mmol/l [14–44], blood concentration 4.35 mmol/l [0.38–35.2], coma (48%), and acute renal failure (42%)) and 14/18 with methanol (pH 7.36 [7.19–7.46], anion gap 17 mmol/l [14–27], blood concentration 16.6 mmol/l [6.8–90.7] and ocular signs (22%)). Fomepizole (1–11 doses) was administered according to the recommendations in 35/53 cases (66%) and associated to hemodialysis in 19/53 cases (36%). Three methanol-poisoned patients presenting concentration >16 mmol/l on admission had favorable outcome without dialysis. There was no worsening of renal function or ocular injuries after Fomepizole initiation. Death rate was 8% (4/53), secondary to mutiorgan failure present on admission. Safety data were available for 49 patients (36M/13F, 5 children) showing ADRs in 5 patients (9%): local intolerance (pain and venous inflammation at the injection site) in 2 cases, facial erythema in 1 case, hypereosinophilia in 1 case, and transient thrombopenia in 1 chronic alcoholic. *Conclusions:* Prognosis of toxic alcohol poisonings remains severe (death rate: 8%), due to late diagnosis and treatment. Fomepizole appears to be well tolerated, with no report of serious or unexpected ADRs

during 2 years in France. However, long term data capture is required to ensure a robust post-authorization safety monitoring for this orphan drug.

192. Paracetamol Poisoning with Fulminant Hepatic Failure in Spite of Adequate Early Treatment with Intravenous Acetylcysteine

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Introduction: Acetylcysteine is an effective treatment for paracetamol (acetaminophen) poisoning, provided it is given sufficiently early. Severe hepatotoxicity is unusual if patients begin antidotal treatment within 8 h of overdose. This is a report of a case of fulminant hepatic failure requiring liver transplantation in spite of adequate early acetylcysteine therapy. *Case History:* A 37 y old female presented 2 h following a stated overdose of paracetamol 30 g and methadone 60 mg. The timing of the overdose was well documented as she had taken this following a psychiatric appointment. There was a past history of resistant depression, recurrent self-harm, anorexia nervosa, previous intravenous heroin use and possible temporal lobe epilepsy. She was an occasional binge drinker. On examination there were superficial lacerations on her wrists. Her pulse was 97/min and blood pressure 125/93. Her abdomen was non-tender. Blood results taken 4 h 15 min after the overdose showed a paracetamol concentration of 302 mg/L and prothrombin time of 13 s. In view of her apparent overdose and the presence of multiple risk factors she was started on intravenous acetylcysteine before her blood results were available and 5 h 5 mins following the stated time of overdose. She received a normal intravenous regimen without problem except that the second bag was infused over 6 h rather than 4 h because of difficult intravenous access. At 30 h after the overdose her PT had increased to 30 s. At 50 h the PT was 106 s with alanine transaminase 23800 U/L and creatinine 143 micromol/L. Acetylcysteine had been continued throughout. She was treated with intravenous vitamin K and referred for hepatic intensive care and urgent orthotopic liver transplantation which she underwent later that day. She made a routine recovery from this procedure. *Conclusions:* Early treatment with intravenous acetylcysteine in recommended doses is not fully effective at preventing fulminant hepatic failure. This patient may have been at very high risk because of her history of anorexia nervosa, carbamazepine treatment and binge drinking. Treatment in advance of the availability of plasma paracetamol concentrations should be considered in patients at particular risk because of the presence of multiple possible risk factors. Further research to establish the frequency of this occurrence would be useful.

193. Recurrent Seizure and Sustained Encephalopathy Associated with DMSO

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Objective: Dimethyl sulphoxide (DMSO) is universally employed in the cryopreservation of stem cells used in autologous bone marrow infusion. We report the case of a patient who developed neurotoxic manifestations following two infusions of DMSO cryopreserved autologous stem cells. *Case Report:* A 49-year-old man diagnosed as having vertebral lymphoma in 2001 was treated with chemotherapy and achieved a complete remission. Stem cells were collected after the first courses of chemotherapy and were preserved with DMSO in liquid nitrogen. In February 2004, the patient developed an abdominal relapse of the lymphoma and was treated again with chemotherapy. New stem cells were collected and preserved in DMSO. An autologus stem cell infusion was performed. A few minutes after the beginning of the infusion, the patient developed a generalized tonic-clonic seizure. The infusion was stopped and the patient received phenytoin and diazepam. He was referred to the intensive care unit (ICU). The remaining stem cells were infused after washing off the cells to avoid DMSO contamination. No neurological adverse event was associated with this transfusion and the patient was transferred to the hematology unit. Seventeen days after this first neurological event (day +17), the patient was still in profound aplasia without evidence of bone marrow regeneration. Therefore, it was decided to wash the stem cells collected in 2001 collect and to infuse them. The patient developed a new generalized tonic-clonic seizure a few minutes after the infusion was started and was readmitted to the ICU. He received

phenytoin, propofol and also magnesium (the patient was profoundly hypomagnesemic). Renal function, estimated by serum creatinine clearance, was normal. An electroencephalogram (ECG) performed one hour later confirmed the resolution of epilepsy but the patient remained in coma with a Glasgow Coma Score (GCS)<7 and required mechanical ventilation. Brain computed tomography was normal, except for mild brain atrophy. Magnetic resonance imaging performed on day +30 revealed diffuse leukoencephalopathy, with multifocal cortical lesions. After 35 days of ICU stay, the patient's neurological condition gradually improved and on day 52 the GCS returned to 15 with no residual gross neurological deficits. *Discussion:* Isolated cases of encephalopathy have been described following the intravenous administration of DMSO as therapeutic agent and seizures have been also reported after infusion of DMSO cryopreserved stems cells. Our case is documented by neuroimaging. The radiological findings are different from those observed in the reversible posterior leukoencephalopathy caused by other drugs. Clinical recovery and radiological resolution are usually slow.

194. N-Acetylcysteine in Acute Iron Intoxication: Is it Hepatotoxic?

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Iron poisoning is one of the leading causes of death in children due to intoxication. The treatment for acute iron poisoning includes use of desferrioxamine (DFO). However, DFO is expensive, is not available in many hospitals, and its administration may be associated with adverse effects. The exact mechanism of iron effect on the various organs is unknown, although is probably related to free radical formation and the release of oxidant agents. N-acetylcysteine (NAC), an antioxidant, is widely used as an antidote in paracetamol intoxication, and other intoxications, such as carbon tetrachloride, paraquat, acetaldehyde, and in diabetic patients undergoing contrast media injection. It is inexpensive and easily accessible, and its administration is associated with only mild adverse reactions. *Objective:* To determine whether orally administered NAC might affect the glutathione-system enzymes in the liver and erythrocytes and reduce mortality of rats following acute, toxic, oral doses of iron. *Methods:* Rats were administered 400 mg/kg elemental iron orally (Group I), corresponding to LD30 in the species tested. Group II received the same oral dose of iron followed by oral NAC 140 mg/kg. Rats in groups III and IV received NAC only or distilled water, respectively. *Results:* Serum iron levels were significantly higher among rats in group II (Iron+NAC), [1516±1280 (385–4842) mg/l] as compared to rats in group I (iron only) [174.5±32.4(133–217) mg/l] ($p<0.001$). AST was higher in group II [254±78(140–403)] IU/L as compared to group I [154±44(116–284)] IU/L ($p=0.007$). Glutathione-system enzymes in the liver and erythrocytes (GSH, GST and GPX) were significantly lower among rats in group II as compared to group I ($p=0.02$, 0.01, and <0.001, respectively). Mortality in group II was significantly higher after 2, 6 and 24 hours as compared with group I [35% vs 8.5% ($p<0.001$); 37% vs 10% ($p<0.001$), and 45% vs. 14%($p<0.001$), respectively]. No deaths were observed among rats in group III and IV. *Conclusions:* The administration of NAC probably increased the absorption of iron through the gastrointestinal tract, causing higher serum iron levels, with significant hepatic damage as reflected by elevated AST and depleted glutathione-system enzymes, and higher mortality rate. We conclude that the administration of NAC in acute iron intoxication in rats might have a negative effect. *Acknowledgement:* The study was supported by The Chief Scientist—The Ministry of Health.

195. Prevalence of Hypersensitivity Reactions to Intravenous N-Acetylcysteine in Acetaminophen Poisoned Patients

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Introduction and Objectives: In patients with acetaminophen poisoning, N-acetylcysteine (NAC) is used as an antidote. Acetaminophen poisoning is the forth cause of drug poisoning in Poisoning Emergency Department of Noor Hospital, and NAC is used by intravenous route (IV). The side effect of IV NAC therapy is anaphylaxis or anaphylactoid reactions. The purpose of this study was to evaluate the prevalence of anaphylacoid or anaphylaxis reactions to IV NAC therapy in acetaminophen poisoned patients and identify previous history of allergy as a probable risk factor. *Methods:* An antrograde study was carried out in Poisoning Emergency Department of Noor Hospital, Isfahan, Iran from September 2003 to

September 2004. A checklist filled for 173 patients with acetaminophen poisoning received NAC by intravenous route. The data were analyzed by chi-square test. A p values less than 0.05 were considered significant. *Results:* The prevalence of side effects to IV NAC was 44.5%. The side effects to IV NAC were nausea and vomiting (63.15%), flashing (30.26%), bronchospasm (26.31%), vertigo (23.68%), skin rash (32.36%) and hypotension (15.75%) respectively. Forty one percent of patients had previous history of allergy. The prevalence of allergy was hyperreactive airway disease (30.69%), skin allergy (17.82%), food allergy (10.89%) and drug allergy (0.99%) respectively. Among patients with previous history of allergy, 83.13% developed side effects to NAC. There was a correlation between previous history of allergy and anaphylactoid reaction to NAC. *Discussion:* Different types of allergy must be considered a risk factor in the development of side effects to IV NAC-therapy. *References:* 1. Perry H, Shannon MW. Acetaminophen. In: Haddad LM, Shannon MW, Winchester JF. Clinical management of poisoning and drug over dose. Philadelphia: WB Saunders; 1998: 664–673.2. Shannon MW, Haddad LM. The emergency management of poisoning. In: Haddad LM, Shannon MW, Winchester JF. Clinical management of poisoning and drug over dose. Philadelphia: WB Saunders; 1998: 2–28. 3. Schmidt LE, Dalhoff K. The Risk factor in the development of adverse reactions to N-acetylcysteine in patients with paracetamol poisoning. *Br J Clin Pharmacol* 2000; 51:87–91. 4. Mant TGK, Tempowski JH, Volans GN, Talbot JCC. Adverse reactions to acetylcysteine and effects of overdose. *Br Med J* 1984; 289:217–219. 5. Vale JA, Proudfoot AT. Paracetamol (acetaminophen) poisoning. *Lancet* 1995; 346:547–552. 6. Flanagan RJ, Meredith TJ. Use of N-acetylcysteine in clinical toxicology. *Am J Med* 1991; 91:131–139. 7. Reynard K, Riley A, Walker BE. Respiratory arrest after N-acetylcysteine for paracetamol overdose. *Lancet* 1992; 340:675. 8. Ho SW-C, Beilin LJ. Asthma associated with N-acetylcysteine infusion and paracetamol poisoning. Report of two cases. *Br Med J* 1983; 287:876–877. 9. Bailey B, McGuigan MA. Management of anaphylactoid reactions to intravenous N-acetylcysteine. *Ann Emerg Med* 1998; 31:710–715.

196. *In Vivo* Radioprotective Efficiency of Fullerenol $C_{60}(OH)_{24}$

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Objective: In vitro studies have demonstrated that fullerenol, a polyhydroxylated derivative of fullerene (C_{60}(OH)n n=12–26), has a high antioxidative potential. Since radiation injury is mainly a consequence of the action of free radical species, the aim of this study was to examine radioprotective efficiency of fullerenol in whole-body irradiated mice and rats. *Methods:* The experiment was performed on adult male white mice and adult male Wister rats, whole-body irradiated with X-rays in single doses of 6 Gy to 8 Gy. Fullerenol was given in doses of 10 mg/kg and 100 mg/kg i.p., 30 minutes before irradiation. The experimental groups consisted of 25–30 mice or 10 rats each. In an experiment, performed on rats whole-body irradiated with X-rays in a single dose of 8 Gy, the radioprotective efficiency of fullerenol was compared with that of the well-known radioprotector amifostine, given in a dose of 300 mg/kg i.p., 30 minutes before irradiation. The survival rate of irradiated animals and body mass gain were monitored over 30 days after irradiation. The mean lethal times (LT50) of irradiated animals were calculated for each radiation dose used and mutually compared. *Results:* The results showed that fullerenol produced a significant radioprotective effect only when given in a higher dose tested (100 mg/kg). In fullerenol-protected mice and rats the survival rate and LT50 were significantly increased compared to those in the control, unprotected animals. This effect was similar to that produced by the standard radioprotector amifostine. *Conclusion:* These results imply a potential use of fullerenol as a radioprotective substance. *References:* Sayes C, Fortner J, et al. The differential Cytotoxicity of water-soluble fullerenes. *Nano Letters* 2004. *In press*. Prylutaskyy Y, Yashcuk V, et al. Biophysical studies of fullerene-based composite for bio-nanotechnology. *Material Science and Engineering C* 2003; 23:109–111. Dugan L, Lovett E, et al. Fullerene-based antioxidants and neurodegenerative disorders. *Parkinsonism and Related Disorders* 2001; 7:243–246. Ueng T, Kang J, et al. Suppression of microsomal cytochrome P450-dependent monooxygenases and mitochondrial oxidative phosphorylation by fullerenol, a polyhydroxylated fullerene C_{60}. *Toxicology Letters* 1997; 93:29–37.

197. Melatonin Reduces Mercuric Chloride-Nephrotoxicity in the Rat

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TABLE 1
Temporal effects of melatonin and mercuric chloride in rat proximal tubules

	C	Melatonin	24 h T3.5-	24 h T3.5+Melatonin	48 h T3.5	48 h T3.5+Melatonin
Normal	86.6±7.2	84.8±7.3	7.6±2.1*	38.7±3.1*+°	12.4±3.8*+	44.3±3.2*+°
Single-cell damage	10.9±4.6	12.9±3.4	23.1±3.3*	33.4±3.6*+	26.3±5.8*	31.2±4.2*+°
Focal atrophy	2.5±0.8	2.3±0.8	39.9±4.1*	19.7±3.2*+°	41.2±8.6*	13.2±3.6*°
Extensive atrophy	0±0	0±0	29.4±4.2*	8.2±3.2*+	20.1±5.3*	11.3±3.2*+°

Data represent means±SD, *$p<0.05$ vs. C; +$p<0.05$ vs. T3.5-24 h; °$p<0.01$ vs. T3.5-48 h. No differences were found between C and melatonin groups using ANOVA and Bonferroni's test.

Objective: It is difficult to clinically differentiate and treat acute renal toxicity from ischemic injury. Mercuric chloride induces an established tubular injury after a single-exposure (1). Melatonin is an effective free radicals-scavenger against mercury-induced nephrotoxicity as reported in a recent biochemical study (2). Metallothionein (MT) is a protein with high affinity for metals that protects the kidneys against oxidative stress (3). Heme oxygenase 1 (HO1) and bcl2 have been detected in proximal tubules affected by a low mercury-dose (1/10 LD50) (4). This ultrastructural study was aimed to better clarify the role of melatonin against nephrotoxicity induced by a high mercury-dose (1/3 LD50). The tubular distribution of MT, HO1 and bcl2 was analyzed by immunohistochemistry. Morphometry was performed to quantify tubular damage. *Methods:* Wistar rats were treated by a single i.p. injection as follows: Group 1—Mercuric chloride, 3.5 mg/kg (T3.5); Group 2—Melatonin, 5 mg/kg; Group 3—Melatonin 30′ before mercury; Group 4—Saline (as C-group). After 24 h and 48 h, kidneys were removed and processed for electron microscopy and immunohistochemistry. *Results:* Melatonin often preserves ultrastructure and limits tubular damage (Table 1). At 24 h, MT is overexpressed in the proximal tubules in the T3.5 group but, after melatonin administration, it is translocated to the distal tubule. At 48 h, MT is restricted to the brush border in the T3.5 group and became faint and cytoplasmic after melatonin supply. Tubular HO1 and bcl2 expressions were very low in controls, intense in the T3.5 group, attenuated after melatonin administration at 24 h. *Conclusion:* These data emphasize the beneficial role of melatonin against mercury-nephrotoxicity in the rat and the early involvement of metallothionein as detoxification marker in specific tubular sites. *References:* 1. Stacchiotti A, et al. *Histol Histopathol* 2004; 19:1209–1218. 2. Sener G, et al. *Pharmacol Toxicol* 2003; 93:290–296. 3. Satoh M, et al. *J Pharmacol Exp Therap* 1997; 283:1529–1533. 4. Nath K, et al. *Kidney Int* 1996; 50:1032–1043.

198. Diagnostic Value of On-Site Immunoassay Screening in Suspected Poisoning: A Prospective Study in the Emergency Department of a Tertiary Urban Hospital

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Objective: On-site tests based on immunoassay techniques are widely used for toxicological screening analysis in patients with suspected poisoning. However, such assays usually have been validated using urine samples with known concentrations of the investigated substances. This type of experiments showed most dependable and reproducible results for the Triage®8 Panel (1) which therefore should be evaluated in a clinical setting in the present investigation. *Methods:* This was a prospective study conducted from January to December 2003 in the emergency department of the University Hospitals Mainz, Germany—an academic tertiary care hospital. For all patients presenting with suspected poisoning, an on-site toxicological screening of urine samples was performed using the Triage®8 Panel (Biosite, Willich, Germany). This procedure indicates the possible presence of amphetamines, barbiturates, benzodiazepines, cocaine, methadone, opiates, tricyclic antidepressants and cannabinoids. For confirmation and further screening analysis, the collected urine samples were investigated by gas chromatography-mass spectrometry (GC-MS) after acid hydrolysis, liquid–liquid extraction and acetylation. Cannabinoids were presently not confirmed. *Results:* A total number of 111 patients were included (54 female, 57 male, average age 37.8±19.7 years). The analysis of the immunoassay and GC-MS results revealed that in 11 patients (9.9%) no relevant toxic substance could be detected (mostly caffeine, nicotine). In 41 patients (36.9%), the only substances present in the urine were those which were undetectable by immunoassay (mostly non-steroidal anti-inflammatory drugs, non-tricyclic antidepressants, opioids). For the

remaining 59 patients (53.2%), the Triage®8 Panel showed 66 correct results for substances which could be confirmed by GC-MS (excluding cannabinoids). Additionally, the Triage®8 Panel yielded 15 false positive and 9 false negative results. False positive or false negative results were not limited to specific substances. *Conclusion:* In view of the present findings on-site immunoassays could no longer be recommended for toxicological screening analysis in patients with suspected poisoning as only every second patient had ingested substances which were principally detectable by immunoassays. In addition, more than 1 in 4 of the obtained results were false. *Reference:* 1. Peace MR, Tarnai LD, Poklis A. Performance evaluation of four on-site drug-testing devices for detection of drugs of abuse in urine. *J Anal Toxicol* 2000; 24:589–594.

199. Alcohol and Illicit Drug Use Among Adolescents Presenting to the Emergency Department

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The highest risk of illicit drug use is between the ages of 12 and 25 years. All epidemiological studies of adolescent alcohol and illicit druge use (AIDU) in Israel to date have been conducted in schools, households and shelters for high risk teenagers. *Objective:* To characterize the teenager that presents to the emergency department (ED) of a general hospital with regard to the presenting complaints, demographic and socioeconomic characteristics, and the use of particular drugs. *Methods:* The study was conducted in two stages: (1) Retrospective, where the charts of children under 18 who had presented to the ED at ''Assaf Harofeh'' Medical Center between 01/01/95 and 31/01/2002 were reviewed and (2) Prospective phase, collecting information about all adolescents who presented to the ED between 01/02/2002–30/06/2003. *Results:* 30 charts were identified retrospectively and 42 in the prospective phase. The average age was 16.7 years. 17 patients (24%) were of Russian extraction, 21% Arab, 10% Ethiopian and 41% were of other Jewish origin. 27 patients (37.5%) learned in secular educational institutions, 6 learned in religious educational institutions and 5 were in residential institutions. 17 were not currently studying at all. 50% used drugs, 43% drank alcohol and 10% did both. The most frequently used drug was marijuana—12 (28%), 10 (23%) used hashish, opiates—7 (16%), ecstasy—7 (16%), hallucinogens—4 (9%), and amphetamines—4 (9%). 6 patients used more than one drug. The most common presenting complaints were related to the effect of the drug on the central nervous system (41.6%), followed by gastrointestinal complaints (12), suicide attempts (9) and 2 with fainting episodes. On presentation, 52 (72%) patients were fully conscious, 16 were semi-conscious and 2 were unconscious. *Conclusions:* Prospectively, 42 patients were found during 17 months as compared to 30 patients in the retrospective part (5 years). This difference is most likely due to the awareness of the ED staff of the search for AIDU. It is possible that AIDU use is in fact rising in Israel. Most of the adolescents were from lower socioeconomic levels, new immigrants, or from poor Arab neighborhoods. However, members of well-established families were also represented. AIDU is not unique to secular society but has in fact reached religious high schools as well. There is a need to invest efforts among the hospital staff and in particular those working at the Emergency Department in order to increase their awareness to the problem. Acknowledgement: The study was supported by The Israel National Antidrugs Authority.

200. Clinical Versus Laboratory Identification of Drugs of Abuse in Patients Admitted for Acute Self-Poisonings

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Objective: The extent of drug abuse in patients admitted for self-poisonings is uncertain. The aim of this study was to assess the pattern of drugs of abuse among patients admitted for acute poisoning according to age and gender, and to study the concordance between the clinical assessments by the physicians on duty and the drug analyses. *Methods:* Prospective study of all patients (n=405, 52% males, median age 31 years) treated for acute poisoning in our department during one year (2001). The physician on call classified type of drug of abuse by history and clinical assessment. This was later compared to urine and blood samples analysed for ethanol, benzodiazepines, opiates, cocaine, ecstasy, GHB, amphetamine and cannabis. *Results:* In 320 admissions

(80%) the comparison between clinical diagnosis and laboratory analyses could be performed. A total of 478 drugs were suspected and 621 were found. The main toxic agents found were benzodiazepines (49.7%), ethanol (40.3%), opiates (35.3%), cannabis (23.8%) and amphetamine (21.3%). The agreement between clinical assessments and laboratory findings was best for GHB and ethanol (kappa=0.43), and for opiates (k=0.38). For benzodiazepines and cannabis, the concordance was poor (k=0.18 and 0.10, respectively). *Conclusions:* Drugs of abuse were more frequently found than suspected clinically, and 92% had used such drugs. Benzodiazepines, ethanol and opiates were most common. The agreement between clinical assessment and drug analyses was moderate to low. Physicians seem to underestimate the use of these drugs.

201. Hallucinogenic Tryptamines: A Case Series

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Objective: The Swedish Poisons Information Centre has noted an increase of inquiries regarding intentional use of hallucinogenic tryptamines during recent years (Table 1). This report summarizes significant symptoms recorded in a case series. *Case Series:* This case series includes all the 13 cases from the period 2002–2004 in whom sufficient clinical data were obtainable. Four of the 13 patients had taken the tryptamine derivative 5-MeO-AMT, six had taken 5-MeO-DIPT and the

TABLE 1
The total number of inquiries to the Swedish Poisons Information Centre regarding hallucinogenic tryptamines[#] 2000–2004

	2000	2001	2002	2003	2004*
Number of inquiries	1	1	2	24	20

[#]Hallucinogenic mushrooms containing hallucinogenic tryptamines not included.
*Until 2 November.

TABLE 2
Significant symptoms in 13 patients after intake of hallucinogenic tryptamines

Age/Sex	Agitation	Hallucinations	Mydriasis	CNS-depression	Repeated seizures	Serious circulatory disturbances
5-MeO-AMT (5-methoxy-alphamethyltryptamine)						
14 y/M	+	−	+	+	+	−
17 y/M	−	+	+	+	+	−
17 y/F	+	+	+	+	+	−
21 y/M	+	−	+	+	+	−
5-MeO-DIPT (5-methoxy-diisopropyltryptamine)						
<28 y/M	+	+	−	−	−	−
<28 y/M	+	+	−	−	−	−
18 y/M	−	−	−	+	−	−
19 y/M	−	+	−	−	−	−
23 y/M	−	−	+	−	−	−
20 y/M	−	−	−	−	−	−
AMT (alphamethyltryptamine)						
21 y/M	+	+	+	−	−	−
27 y/M	+	−	+	−	−	−
20 y/F	+	−	+	−	−	−

Analysis of confiscated powder was positive for 5-MeO-AMT.

remaining three had ingested AMT (Table 2). All the patients were below the age of 28 (14–27). In at least ten of the cases the drug was purchased over the Internet. Significant symptoms recorded during the hospitalization are presented in Table 2. More infrequent or unspecific symptoms noted were: redness of the skin, nausea, vomiting, haematemesis, dizziness, confusion, sensation of numbness, tremor, anxiety, mild hyperthermia, sweating, mild tachycardia, mild hypertension and breathing problems. Treatment was symptomatic. In a few cases general anaesthesia and mechanical ventilation combined with administration of antiepileptic drugs was carried out to control seizures. The patients were hospitalized for a maximum of two days and the outcome was satisfactory in all 13 cases. *Discussion:* The clinical features seen in our case series are in accordance with the present literature, in which only a few full case reports (1–3) and some abstracts have been published until now. *Conclusion:* An increasing use of hallucinogenic tryptamines is seen in Sweden. These drugs are easily bought on the Internet and are commonly used by younger persons. Hallucinogenic tryptamines can give rise to severe CNS-symptoms, but their cardiovascular toxicity seems mild. Our case series indicates a higher CNS-toxicity of 5-methoxy-alphamethyltryptamine compared to the other derivatives. However, the material is limited and further observations are needed to confirm this finding. *References:* 1. Long H, et al. *Vet Hum Toxicol* 2003; 45:149. 2. Meatherall R, et al. *J Anal Toxicol* 2003; 27:313–317. 3. Brush DE, et al. *J Toxicol Clin Toxicol* 2004; 42(2):191–195.

202. Failed Whole Bowel Irrigation in Heroin Body Packer: Late Endoscopic Removal of the Packages

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Background: Whole bowel irrigation (WBI) is standard and very efficient treatment method used for gastrointestinal decontamination of nonobstructed body packers. Majority of body packers can be treated conservatively using WBI, naloxone, and promotility agents. Obstructed and symptomatic patients are treated surgically. Endoscopy is used very rarely due to wide spread fear of rupturing packages and complicating hospital course. *Case Report:* A 42 year old woman without previous medical history was found unresponsive in the cab upon arrival from the Latin American country. In the ED patient was found to be in opioid overdose, and diagnostic imaging revealed intestines full of regularly shaped packages. Patient was temporarily intubated, started on IV naloxone drip, and WBI was initiated with Golytely at the rate of 2 L/hr. Next day patient was extubated and asymptomatic. Over 3 days, she received total of 130 L of Golytely and passed only one broken package. Golytely was stopped and patient was started on promotility agents: metoclopramide (10 mg every 6 hr) and erythromycin (500 mg every 6 hr) for 48 hours without any result. On day 5 of her hospitalization she was still asymptomatic and therefore not surgical candidate. GI service initially refused to perform endoscopy, and after 3 attempts they were able to remove all packages. Endoscopy did not reveal any stenotic changes or polyps. No package was broken during the procedure. *Conclusion:* Even extensive WBI with the use of promotility agents and IV naloxone can be unsuccessful in the removal of drug packages from the GI tract. Endoscopy should be considered because it is less invasive than surgery, and quality of the packages is significantly improved, so the risk of the rupturing is very low.

203. Fatal Sepsis with Multiorgan Failure Due to Accidental Urine Injection in a Drug Addict Case

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Objective: Local and even systemic inflammation associated with i.v.-injections in drug addicted cases is common. Although in-hospital treatment is sometimes lengthy outcome is usually favourable and fatal courses are rare. We report on an unusual case of accidental i.v.-injection of urine. The patient developed a fulminant Gram-negative sepsis with multiorgan failure and disseminated intravascular coagulopathy with an ultimately fatal course. *Case Report:* A 33-year old drug addict patient injected accidentally 5 ml of her own urine (drug-free urine kept cool over one week for unanticipated drug-screening) in the femoral vein. She had confused it with her take-home dose of methadone, stored in a similar bottle. Soon after injection she was found confused with shivering and seizures. On admission she was disorientated with blood pressure of 90/60 mm Hg, heart rate of 120/Min and fever of 39.5°C. Laboratory tests showed signs of consumptive coagulopathy, leukopenia and electrolyte disorder. Because of respiratory depression the patient was intubated and mechanically ventilated. Escalating empirical antimicrobial

treatment started with vancomycin, imipinem and fluconazol the first two days reduced to imipinem after evidence of *Escherichia coli* and *Klebsiella pneumoniae* in blood cultures. Severe coagulopathy was effectively treated with tranexamic acid (500 mg i.v. over three days), PPSB and fresh frozen plasma. Vasopressors (norepinephrine and dopamine) were used to maintain mean arterial pressure above 65 mm Hg. Acute renal failure required haemodialysis and ultrafiltration. Corticosteroid treatment with hydrocortisone (240 mg/die) was applied for 8 days. The further course was complicated due to gastrointestinal bleeding and peritonitis with evidence of bacteroides species in ascites fluid. Laparotomy revealed perforation of terminal ileum (mainly due to ischemic bowel lesions) with the need for partial ileum-resection. The patient could be weaned from mechanical ventilation eventually on day 18 with an initially uneventful further course. On day 25 the patient developed a cardiac arrest with primary successful resuscitation but electromechanical dissociation lead to death on day 26. Post-mortem autopsy showed a rough left ventricle without signs of ischemic lesions or the initial expected pulmonary embolism. Origin of myocardial alteration remains unclear. *Conclusion:* Although serious systemic inflammation associated with i.v.-injection in drug addict patients is rare, one has to be aware that septic courses sometimes occur. The moderately intoxicated person is especially at higher risk of confusing narcotics. This case of Gram-negative sepsis is quite similar to the experimentally induced sepsis-models in animals—mainly by infusion of *Escherichia coli*. To our knowledge it is the first case of i.v.-injection of urine followed by sepsis and multiorgan failure described in literature.

204. Reports of GHB and Related Drug Exposures in California: A 5-Year Review of Poison Control Center Data

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Background: Since the first reports of gamma-hydroxybutyrate (GHB) abuse appeared in the early 1990's, changing use patterns have led to differing at-risk populations, use of precursor chemicals, and types of adverse effects. In 2000, GHB became a Controlled Substance in the US and in 2002, Internet sources of GHB and GHB-precursors were further restricted. Because of these changes, we hypothesized the total incidence and relative distribution of GHB related exposures reported to California Poison Control System (CPCS) would reflect these factors. We undertook a formal retrospective review of all GHB and GHB-precursor case details reported to CPCS to analyze these temporal trends. *Methods:* We conducted a retrospective review of all computerized CPCS case records involving suspected exposures to GHB and its precursors (gamma-butyrolactone, butanediol, and gamma-valerolactone) covering January 1, 1999 through December 31, 2003. Eligible case records were identified using American Association of Poison Control Centers (AAPCC) generic and product codes for all known chemical, commercial and slang names for GHB and GHB-precursors (160 possible codes). In addition, an expanded computerized search of the database was conducted to capture any case record with open-ended text noting GHB, GHB-precursor names, or the descriptive words ''rape'' or ''assault'' (to better identify GHB-facilitated malicious events). *Results:* After excluding duplicates and unrelated or non-exposures 1339 incident cases were identified for analysis over the 5-year study period (Table 1). There was a sharp overall decline of 76% in total case reporting over the study period, moreover, the proportional decline appeared to accelerate each year (18%; 21%; 33%; 45%, sequentially). Total CPCS reports of human exposure calls were relatively stable over this period, with the mean yearly incidence 222,262+8,906. Despite the decline, demographic and case-severity mix did not demonstrate a

TABLE 1
Yearly GHB cases by outcome category

	Total (n=1339)	1999 (n=428)	2000 (n=349)	2001 (n=276)	2002 (n=184)	2003 (n=102)
Female, n (%)	603 (45%)	163 (38%)	159 (46%)	136 (49%)	83 (45%)	62 (61%)
Age, mean±SD	27±9.0	26±9.1	27±9.3	26±8.5	28±9.1	26±7.7
Outcome, n (%)						
No/Minimal	401 (30%)	100 (23%)	122 (35%)	86 (31%)	54 (29%)	39 (38%)
Moderate	793 (59%)	282 (66%)	206 (59%)	151 (55%)	99 (54%)	55 (54%)
Major/death	145 (11%)	46 (11%)	21 (6%)	39 (14%)	31 (17%)	8 (8%)

significant secular trend over the study period. *Conclusion:* GHB case incidence detected through poison control center surveillance appears to have fallen off notably in recent years. Although the overall demographic and case-severity mix appears to be stable, patterns among sub-groups of GHB exposed persons (e.g. frequent users who become dependent or experiencing malicious ingestion) warrant further analysis.

205. QT Prolongation and Torsades Associated with Methadone Therapy

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Background: Methadone is commonly used for opioid dependency and chronic pain, often at high daily doses. Though not considered a pro-arrhythmic drug, there are rare reports of patients taking methadone (typically higher than 100 mg/day) developing prolongation of the QT interval and Torsades de Pointes (TdP). We report a case of a patient with methadone-induced QTc prolongation and TdP. *Case Report:* A 52-year-old woman receiving 125 mg/day of methadone for opioid dependency presented to the ED after a syncopal episode. In the ED her QTc was measured at 517 milliseconds (msec), and she developed ventricular ectopy with transient runs of TdP. Laboratory data revealed a magnesium level of 1.3 mEq/L and potassium level of 3.2 mEq/L. She was treated with 2 grams IV magnesium and 100 mg IV lidocaine. During her admission she experienced an episode of pulseless TdP. CPR was performed, and the patient was successfully cardioverted with 200 Joules; QTc was 675 msec, magnesium and potassium concentrations were normal. Cardiac and pharmacological work-up revealed a tricuspid valve mass but no other cause for the QTc prolongation or dysrhythmias. Her methadone dose was decreased to 80 mg/day and follow up EKG revealed normalization of the QTc interval. *Conclusion:* Methadone therapy may have a dose dependent effect on cardiac repolarization resulting in QT prolongation and the risk for ventricular dysrhythmias.

206. *Cannabis sativa* Paediatric Poisonings in Spain

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Introduction: Cannabis sativa is a plant used worldwide both as a drug of abuse and for therapeutic purposes. The most significant psychoactive cannabinoid is 1-delta-9-tetrahydrocannabinol (THC). Metabolites of THC can be found in plasma, feces, and urine. Severe poisonings after ingestion are not frequent among adults, but marijuana should be considered dangerous for children and could require close monitoring for several hours. The objective of this review is to describe the marijuana intoxications in young children ($\leq$7 years old) detected by our Poison Control Centre. *Case Series:* Thirty-five cases of marijuana exposures in young children were registered by our service between October 1993 and October 2004, involving 22 male and 13 female with a mean age of 24 months (range 3 months-7 years old). The drug was ingested alone in 31 cases, and in combination with other substances in 4 cases [tobacco (3), and cocaine (1)]. The consults came from health care units in 30 cases, and the rest from the general public. At the time of the consult, 3 cases were asymptomatic, 4 patients had mild symptoms, moderate cases accounted for 16, and severe for 12. Toxicological screening tests were performed in 8 cases with positive results for cannabinoids in urine. The ingested dose of drug ranged from a few milligrams to 3 grams. All cases were oral exposures, and occurred at home in 29 cases, 2 cases in parks, and one case at school. The clinical manifestations were: Neurological—drowsiness (17), hypotonic (5), coma (4), irritability alternating with somnolence (4), ataxic gait (3), stupor (2), disorientation (1), tremor (1), dystonic movements (1); Cardiovascular—tachycardia (4), hypotension (2); Gastrointestinal—nausea (2), vomiting (1), abdominal pain (1); Ocular—mydriasis (4), miosis (2); and other signs—pallor (2), fever (2), cyanosis (1), conjunctival hyperemia (1). In one case of coma, naloxone and flumazenil were administered at the hospital, with no response, before demonstrating the presence of cannabinoids in the toxicological screen, and before consulting our service. *Conclusions:* Rare cases of marijuana intoxication are described in infants in our country, despite the high incidence of consumption among the general population. In many young children CNS depression occurred after marijuana ingestion. As the success of treatment relies on the differential diagnosis of coma, cannabinoids should specifically be screened for in cases of coma whenever drug ingestion is suspected in the paediatric population.

207. Poisonings by Plants with Psychotropic Effects. Special Mention to Intentional Abuse in Spain

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Objective: Although plant intoxications reported to the Spanish Poison Control Centre (SPCC) represent only 1% of toxic exposures, they can produce severe intoxication, especially those acting on the CNS. Some of these plants can be used as substances of abuse, especially among young people. The aim of this study is to analyse the circumstances of poisonings due to plants with CNS toxicity, with special reference to intentional abuse cases. *Methods:* SPCC records of all patients exposed to plants with psychotropic effects were reviewed for the past 13 years. *Results:* A total of 442 consults meeting the inclusion criteria were recorded during the study period. There were 49.3% male, female (48.4%), animals (0.5%), and unknown (1.8%). Adults accounted for 62.3%, and children 37.7%. A high percentage (59.1%) were in the range 13–39 years old. Routes of exposure were: oral (98.1%), dermal (0.7%), inhalation (0.5%), ocular (0.5%), and rectal (0.2%). The toxic exposures occurred at home in 80.2% of cases, nature (7%), school (1.8%), street (1.6%), work (0.2%), and unknown (9.2%). Health care units required our medical counselling in 56.4% of cases, general public (43.4%), and veterinaries (0.5%). The number of consults increased in the last 4 years when they represented 54.7% of all cases. Clinical status was asymptomatic/mild in 49.5% of patients, moderate (35.5%), and severe (15%). Aetiology was accidental in 49.4% cases, intentional (47%), and unknown (3.6%). Of the intentional cases: suicidal attempts (44.7%), abuse (39.4%), misuse (7.7%), intentional unknown (7.7%), and homicidal (0.5%). At the time of the call clinical manifestations for the total consults and abuse were, respectively: neurological 32.1% and 53%; gastrointestinal 11.5% and 16.3%, cardiovascular 7.5% and 14.3%, hepato-renal 0.7% and none, dermal 2.2% and 3%, respiratory 1.1% and 5%, haematological 0.2% and 1%, and other 3.4% and 8.1%. Hallucinations were present in 8 *Datura stramonium* intentional abuse cases, *Hyoscyiamus niger* (1), *Atropa belladona* (1), Ayahuasca (1). The main plants involved in abuse cases were: *Datura stramonium* (34.1%), *Valeriana officinalis* (7.3%), *Atropa belladona* (7.3%), *Myristica fragans* (6%), *Ephedra fragilis* (5%), Ayahuasca (3.6%), *Lophophora williamsii* (3.6%), *Hyoscyiamus niger* (3.6%), *Papaver spp*. (2.4%), *Mandragora officinalis* (2.4%), *Argyreia nervosa* (1.2%), *Artemisia absinthum* (1.2%), *Coryanthe yohimbe* (1.2%), *Piper methysticum* (1.2%). *Conclusions:* For plants affecting the CNS, the majority of poisonings were graded as moderate to severe. *Datura stramonium* was the plant most involved in intentional abuse. Educational measures should be put in practice for both health professionals and young people in order to avoid underestimation of the risk of natural toxins.

208. Non-Infectious Retinal Artery Complications in Intravenous Drug Users

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Objective: To identify the products or behaviours that may induce non-infectious retinal artery complications in intravenous drug users. *Method:* Literature review (Medline up to November 2004 and Optometry Today). *Results:* Intravenous drug use may lead to retinal artery complications that can be infectious (bacterial, viral or fungal complications) or non-infectious. Non-infectious complications can be the result of two mechanisms. See Table 1. The first mechanism is embolisation of micro-particles causing the obliteration of retinal arteries. These micro-particles may be either filler materials that have been added to the drug (talc, flour) as a cheap way to increase its weight, or tablets that have been crushed and injected after partial dilution and filtration. In the literature, the tablets involved in talc retinopathies are: methylphenidate Ritalin®, pentazocine Talwin®, codeine, methadone, meperidine. Intravenous injection, most often in the bend of the elbow, can cause embolisation of these particles to the pulmonary circulation. Particles above 5–10 microns are retained by the lungs, therefore causing pulmonary granulomatosis that may lead to hypertension. Smaller particules are not retained by the lung filter and are deposited in the retinal circulation. Retinopathy will depend on the quality of the filtration and on the cumulative number of tablets that have been injected. The second mechanism involved concerns vasomotor disorders such as hypertension or arterial vasospams. Vasospams can affect retinal arteries directly or the cerebral circulation with indirect repercussions on the retina due to emboli resulting from the disruption of atheromatous plaques. In the literature, the drugs responsible for vasospasms are cocaine, amphetamines, quinine and possibly buprenorphine hydrochloride Subutex®, due to a paradoxical effect. Buprenorphine usually has hypotensor and cardioprotector effects but this can be reversed in the presence of atheromatous lesions. A case of myocardial infarction has been reported, which suggests that this paradoxical effect of buprenorphine could also lead to retinal

Table 1

Toxic mechanisms	Products involved
Embolisation of micro-particles	Filler materials: cosmetic talc (magnesium silicate), flour Excipients for injected drugs: pharmaceutical talc, magnesium stearate, starch, micro-crystalline cellulose
Arterial vasospasm	Active ingredients: cocaine, amphetamines, opioid agonist-antagonist: buprenorphine hydrochloride Subutex® (possible paradoxical effect) Filler materials: quinine

complications. *Conclusion:* In intravenous drug users, the nature of the products that have been injected and/or the way they have been prepared have an influence on the occurrence of retinal artery complications. Early information from drug users can help reduce risk of complications. *References:* Cracowski JL, Mallaret M, Vanzetto G. Myocardial Infarction Associated with Buprenorphine. *Ann Intern Med* 1999; 130(6):537. Maloney C. Talc retinopathy. *OT* 2002; 42(24):34–36.

209. Reports of Gamma Hydroxybutyrate Ingestions with Motor Vehicle Involvement: A Five-Year Review of Poison Control Center Data

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Objective: Drugs and alcohol are commonly implicated intoxicants found in persons driving under the influence (DUI). Recently, gamma hydroxybutyrate (GHB) and related precursor drugs have been implicated in such events. The true incidence of GHB-related DUIs is uncertain due to non-specific symptoms of GHB intoxication and inconsistent analysis of biologic samples. *Methods:* We conducted a retrospective review of all computerized case records reported to the CPCS involving suspected exposures to GHB and its precursors covering January 1, 1999 through December 31, 2003. Each case was reviewed for open-ended text fields indicating motor vehicle involvement, including DUIs and subjects found unconscious in cars (FIC). These cases were further reviewed for incidence of motor vehicle accidents (MVA), resulting trauma, and co-ingestants. *Results:* We identified 41 (3%) reports of GHB use in persons found DUI or FIC among 1339 GHB cases over the 5-year study period. Of the 41 cases, 13 (32%) were DUI and 28 (68%) FIC. The mean age was 28 (range 17–51 years); 24 (59%) were male. Among the DUI cases, 7 (54%) were associated with vehicular accidents; only two subjects sustained trauma. Nine subjects (22%) had a history of alcohol co-ingestion but only 6 (15%) cases had laboratory confirmation of ethanol. A toxicology screen for common drugs of abuse (DOA) was performed in 20 (49%) patients. Ten (24%) of these patients tested positive for at least one of the following DOA: amphetamines, benzodiazepines, cocaine, marijuana, opiates, and phencyclidine. *Conclusion:* Due to the significant central nervous system depressant effects of GHB such as rapid loss of consciousness, driving under its influence poses a potentially serious risk to public health. Because DUI suspects are not routinely tested for GHB, the actual number of persons driving under its influence is unknown. In addition, such cases are not routinely reported to Poison Control Centers. Therefore, the number of GHB related DUIs and MVAs may be far greater than those identified in our review.

210. Cannabis and Solvents Causing Posterior Leukoencephalopathy

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Objective: Toxic leukoencephalopathy is a structural alteration of cerebral white matter in which myelin suffers the most damage and may be caused by exposure to a wide variety of agents, including therapeutic agents, drugs of abuse and environmental toxins. We present a patient with toxic leukoencephalopathy after consumption of cannabis. *Case Report:* A 42-year-old was admitted to hospital with seizures, altered mental status, headache, and visual disturbances after smoking a new cannabis preparation obtained from Holland and home-grown seeds. He was a craftsman with long-term occupational exposure to spray paints and lacquer, working in poorly ventilated areas at home and used no respiratory or cutaneous protection. He didn't use toluene. He was a heavy cannabis smoker (long-term, daily user, 5–6 cigarettes) with no use of any other drug of abuse or intake of ethanol. He was not using medicinal plants. Physical examination revealed mild left hemiparesia and sensory deficits. He had no fever or elevation of blood pressure. Blood count, blood gases, biochemical parameters, antinuclear, viral and bacterial antibodies, cerebrospinal fluid, screening for others drugs of abuse and heavy metals were within normal values. Cranial CT revealed a white matter of increased density in both occipital and parietal lobes, with edema and contrast enhancement. T2-weighted MRI revealed a diffuse hyperintensity of the white matter of both occipital lobes and right temporary lobe. Diffusion study and angiographic MRI were both normal. Electroencephalography revealed global low activity. The differential diagnosis included: neurodegenerative diseases, anoxia, metabolic encephalopathy, cerebrovascular disease, chronic small vessel disease, infectious disease, traumatic brain injury and other toxic agents. The patient received treatment with dexametasone, manitol, diazepam, valproic acid and phenytoin. During his stay he suffered 3 seizures. He was discharged with symptom improvement, except cortical blindness with normal ophthalmologic exploration. At check-up 6 months later he had cortical blindness and partial resolution of MRI images. *Conclusion:* Toxic leukoencephalopathy should be included in differential diagnosis of acute or chronic neurobehavioral deficits in any patient with potential or known exposure to leukotoxic agents. Cannabis has not yet been reported as a leukotoxic agent but the average THC content of cannabis preparations has been increasing in recent years as a result of sophisticated cultivation and plant breeding techniques that produce high potency subspecies and preparations. There is a cause-effect relation after smoking new cannabis preparations and clinical symptoms. In addition, this patient presented with new seizures after smoking cannabis in the hospital garden. *Reference:* Filley CM, Kleinschmidt-DeMasters BK. Toxic leukoencephalopathy. *N Engl J Med* 2001; 345(6):425–432.

211. Trends in Poisoning with Substances of Abuse Among Danish Youths

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Objective: Studies performed by the Danish health authorities (1) and international bodies (2) have documented an unusual high and increasing use of alcohol and several drugs of abuse among Danish youths. The present study was conducted in order to assess whether poisoning by these substances parallels the high level of use. *Methods:* Survey of the Danish population through the national hospital discharge register. All hospital admissions for drug and alcohol poisoning in the age group 12–25 years during the years 1995–2001 were included. Age and sex specific rates were calculated with the Danish population in the respective groups as denominator. Chi square statistics were used for comparisons of groups and evaluation of trends. *Results:* During the study period 2,199 and 1,145 persons were admitted to hospital for drug and alcohol poisoning respectively, corresponding to average rates at 69.8 and 36.3 pr. 105 person years. Morbidity for males was twice as high as for females for drug poisoning and 60% higher for alcohol poisoning. Drug poisoning increased with age to a stable level at 100 admissions pr. 105 person years from the age of 19 years. Alcohol poisoning was frequent from 13 years—approximately 50 admissions pr 105 person years—and then declined from 17 years to 20 admissions pr 105 person years in the oldest age groups. Morbidity for all drugs of abuse increased from 48 to 105 admissions pr. 105 person years during the study period ($p<0.001$). This was explained by upward trends for poisoning with ecstasy and analogues ($p<0.001$), cannabis ($p<0.001$), cocaine ($p=0.01$) and other drugs of abuse. For opioides the trend was significantly downward during the study period ($p<0.001$) and for alcohol morbidity was constant ($p=0.23$). *Conclusions:* Increasing use of drugs of abuse among Danish youths was associated with increase in admissions to hospital due to poisoning with these substances. Alcohol related morbidity on the other hand remained stable throughout the study period albeit reported increase in almost al parameters of use including having being drunk. *References:* 1. National Board of Health. Report on alcohol, drugs of abuse and tobacco. National Board of Health, Copenhagen 2002. 2. ESPAD. The 1999 ESPAD report: Alcohol and other drug use among students in 26 European countries. www.ESPAD.org.

212. Amitriptyline Poisoning from Intentional Intravenous Injection: Clinical Aspects and Toxicokinetic Data

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Objective: The clinical features and toxicokinetics of amitriptyline were studied in a patient that self injected this antidepressant. *Case Report:* A 30-year-old man with a history of drug abuse and treatment with methadone was found comatose in his bathroom near an empty syringe and a pharmaceutical bottle containing amitriptyline (Laroxyl®). Examination of an antecubital puncture mark revealed IV injection. On Emergency Department arrival, physical examination showed deep coma and miosis, without respiratory failure. The preliminary diagnosis was opiate intoxication. Naloxone administration (0.4 mg intramuscularly and 0.4 mg IV) resulted in generalized seizures. Seizures were resistant to midazolam 25 mg IV, but responded to propofol 2.5 mg/kg IV. After immediate transfer to the Critical Care Unit, he was treated with mechanical ventilation and propofol infusion (6 mg/kg/h). No cardiovascular effects were observed. Twelve hours later, sedation was stopped and the patient extubated. An electroencephalogram was negative. The patient had a good recovery and revealed IV self injection of exactly 3.5 ml of Laroxyl®. Sequential blood samples were taken at 2.5, 4, 6, 10, 13.5, 14, 20, 24, 32, 38, 48, 72 hours post injection. No morphine, cocaine, benzodiazepines or ethanol were detectable in blood. Methadone serum concentration was 800 ng/mL (normal range 50–1000). Morphine was present in urine. In gastric aspirate on admission amitriptyline was absent. Its concentration in the utilized bottle was 40 mg/mL. Amitriptyline and nortriptyline were measured using HPLC-UV. The highest amitriptyline serum concentration (610 ng/mL) was found at 2.5 hours post injection (normal 100–200). In the following hours, a two phase exponential decay was calculated according to the equation: $y\ (ng/mL) = 763\ e[-0.136 \times (hours)] + 97\ e[-0.02 \times (hours)]$. Alpha and beta half-life was 5 and 34 hours respectively. Nortriptyline was present in serum from 13.5 to 72 hours post injection. Its concentration ranged from 40 to 140 ng/mL. *Conclusion:* Toxicological investigations suggested a recent heroin abuse, excluded amitriptyline ingestion and confirmed the IV route of tricyclic poisoning. The knowledge of amitriptyline serum levels was an aid in managing the duration of anticonvulsant therapy. Seizures were due to toxic effects of amitriptyline. We also postulate that naloxone given to antagonise the sedative action of methadone caused up-regulation of the glutaminergic system, and hence a pro-convulsant effect. *Reference:* Mariani PJ. Seizure associated with low-dose naloxone. *Am J Emerg Med* 1989; 7(1):127–129.

213. Reports of Gamma Hydroxybutyrate (and Precursor) Dependence and Withdrawal: A Five-Year Review of Poison Control Center Data

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Objective: Gamma hydroxybutyrate (GHB) and its precursors are addictive and may result in serious toxicity upon abrupt discontinuation in the dependent patient. In 2000, GHB became a Controlled Substance in the United States; limiting its availability. We hypothesized that this decline in availability would result in an increased severity of the withdrawal syndrome identified in this patient population. *Methods:* We conducted a retrospective review of all case records reported to the CPCS involving suspected exposures to GHB and its precursors, gamma butyrolactone, butanediol, and gamma valerolactone. The review covered a five-year period from January 1, 1999 through December 31, 2003. Each computerized case record, including open text fields, was reviewed for a history of GHB dependence and GHB withdrawal symptoms. Dependence was defined as clinical evidence of withdrawal or a history of frequent use (daily or more) indicating tolerance. In addition, text describing the patient as ''dependent'' or seeking detoxification met case criteria for dependence. *Results:* In total, 1339 GHB and related exposure cases were identified. Of these, there were 167 reports of GHB dependence (12.5%), of which 135 (81%) were associated with a clinical course consistent with GHB withdrawal. The mean age was 30±9 (range 17–60 years); 122 (73%) were male. Among the GHB dependent cases, 11 (6.6%) reported use for bodybuilding compared to only 19 (1.6%) of all other cases ($p<0.001$). Similarly, 10 (6.0%) of the dependence cases reported using GHB for insomnia compared to only 16 (1.4%) of all other cases ($p<0.001$). The most commonly reported major neurological symptom among the dependent group was agitation, which was noted in 98 (58.9%) compared to only 162 (13.8%) among all other GHB cases ($p<0.001$). Seventy-one percent of

patients were treated in a health care facility, and, of these, 48% were admitted. The mean hospital stay was 4.5 days±4.3 days. Clinical outcomes according to standard American Association of Poison Control Centers criteria were as follows: no/minimal effect 30 (18%); moderate effect 98 (59%); major effect 19 (11%); death 1 (0.6%), unknown 19 (11.4%). Although total exposures declined over the observation period, the number of patients with severe outcomes for GHB withdrawal increased significantly (10/130 cases in 1999–2001; 10/37 cases in 2002–2003; p value=0.003). *Conclusion:* GHB dependence and withdrawal may result in serious toxicity requiring extended hospitalization. The proportion of serious outcomes in this population is rising.

214. Reports of Suspected Malicious Drug Administration: A 5 Year Review of Poison Control Center Data

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Objective: A number of drugs can be used effectively to facilitate sexual assault and other criminal activities, because they can be administered easily and surreptitiously to unsuspecting victims. Among these, gamma hydroxybutyrate (GHB) and related precursor drugs (GBL, BD, GVL) are believed to be prominent, as well as benzodiazepines, such as flunitrazepam. The true incidence of drug facilitated sexual assault (DFSA), which is a subset of malicious administration cases, is not known due to a lack of consistent reporting. *Methods:* We conducted a retrospective review of all case records reported to the California Poison Control System (CPCS) involving suspected exposures to GHB, GBL, BD, and GVL. In addition, narrative fields in computerized records were searched for the words ''rape'' and ''assault'' to help identify those who suspected being given a drug maliciously and those reporting DFSA events. The review covered a five year period from January 1, 1999 through December 31, 2003. *Results:* A total of 1339 eligible cases were identified. Of these, there were 270 reports of suspected malicious drug administration (20%), of which 52 patients reported being sexually assaulted (4% of total; 19% of malicious cases). The mean age was 26±8 (range 12–58 years); 235 of 270 (87%) victims were female. Ethanol was co-ingested in 115 cases (43%). When the site of exposure was discernable from the case record, 126 incidents (47%) occurred at an entertainment venue, such as bars, clubs, parties. In only 72 cases (27%) was the contact with CPCS made within 12 hours of exposure, a time frame during which GHB could reasonably be detected for forensic purposes. Toxicology screening for drugs of abuse was performed in 33 (12%) of cases. GHB was tested for in only one case and was negative, and benzodiazepines were positive in two cases. Clinical outcomes according to standard American Association of Poison Control Centers criteria were as follows: no/minimal effects, 91 (34%); moderate/major, 170 (63%); and lost to follow-up, 9 (3%). 103 (38%) of victims reported some degree of memory impairment. *Conclusion:* Suspected malicious drug administration typically occurs among females and is characterized by delayed reporting that precludes appropriate forensic testing.

215. Illicit Clozapine for Knock Out Use

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Case Report: 5 female employees of a hotel room service experienced sudden dizziness, sleepiness and ataxia 30 min after having consumed a coffee with sugar in it. They had experienced similar episodes before in the last 6 months. One of them (Patient 1) sought the help of a family doctor and collapsed in his office. There the BP was 80/40 mm Hg the HR 40/min and pinpoint pupils were noted. Soon she regained consciousness and received 1 mg of atropine iv. She was sent to our hospital arriving 2:45 h after having drunk the coffee. Vital signs were stable, she was orientated but still drowsy, showing a slurred speech and ataxia. Consumption of drugs, alcohol or medication were denied. Clozapine was detected in an analytical screening of her urine by an automated HPLC system and confirmed quantitatively by an HPLC with DAD detection in her serum. The results are shown in the Table. The police were informed and brought a sugar bowl that had a yellow-brownish crust. Analysis of it showed clozapine together with sugar. Her colleagues were called into our hospital and arrived 9 h after consumption of the coffee. Their condition was stable, but they reported feeling dizzy. Clozapine was detected in the serum of all patients (Table 1). They went home after counselling. Patient 1 recovered after 21 h. Investigations by the police revealed a member of the room service who admitted having mixed 3 powdered tablets of clozapine with the sugar in the sugar bowl of their cafeteria, as she felt threatened by the others. *Discussion:* clozapine has not previously been reported to be used as a knock out drug, except for one

TABLE 1
Clozapine serum levels

		Time after coffee [h:min]			
	Serum μg/l	2:45	4:45	9:30	23:00
Patient 1	Clozapine	75	55		<20
	Desmethylclozapine	33	<20		<20
Patient 2	Clozapine			5	
Patient 3	Clozapine			9	
Patient 4	Clozapine			8	
Patient 5	Clozapine			11	

fatal case of Munchausen syndrome by proxy (1). However, in Nuremberg a criminal gang used clozapine together with ethanol to intoxicate their victims and subsequently rob them. Between 1995—2003 we detected clozapine in 15 overdosed opiate addicts though they were on no medication for psychotic disorders. 4 of them admitted having purchased clozapine from the illicit market and consumed them with the intention to become inebriated. *Reference:* 1. Bartsch C, et al. 2003 Munchausen syndrome by proxy (MSBP) an extreme form of child abuse with a special forensic challenge. *Forens Sci Internat* 137:147–151.

216. Multiorganic Involvement in a Sniffer of Hair Lacquer. The Significance of Mitochondrial Dysfunction

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Objective: We report on a chronic sniffer of hair lacquer who was twice referred to our hospital due to episodes of agitation and disorientation caused by intoxication by isopropanol and dichloromethane contained in a spray of hair lacquer. *Case Report:* A 41-year-old woman was discovered by her husband suffering from agitation and disorientation after having sniffed hair lacquer for one hour. On admission, the patient was conscious and alert, and the agitation had decreased. The lacquer sniffing had begun a year previously and the abuse was practically a daily occurrence. Vital signs and physical examination were normal. The patient complained of headache. The lacquer contained isopropanol and dichloromethane as solvents, and butane and propane as propellants. Blood concentrations of isopropanol (0.3 g/L) and carboxyhemoglobin (9.2% in a non-smoking patient) were determined. Oxygen therapy was administered for 6 hours and the patient was kept under observation. Clinical progress was satisfactory and the patient was discharged. The patient was readmitted 20 days later due to a similar episode. The concentration of isopropilic alcohol was 0.1 g/L and carboxyhemoglobin 5.2%. ECG showed repolarization anomalies. Oxygen therapy was administered for 4 hours and the patient was admitted for tests, which revealed hepatic function abnormalities (GOT 52 U/L, GPT 72 U/L, GGT 41 U/L), reduced glomerular filtrate (creatinine clearance 68 ml/min), renal tubular dysfunction (N-acetylglucosaminidase 5.92 u/L), reduced CO diffusion in respiratory function tests, and marked attention and concentration deficits on the neuropsychological evaluation. There were no manifestations compatible with a withdrawal syndrome. Study of the mitochondrial function of the lymphocytes showed reduced cytochrome oxidase (complex IV) activity on admission, which was partially recovered at 45 days. This may have been due to repeated elevations of the carbon monoxide concentration as a metabolite of methylene chloride and/or the effect of the two solvents (isopropanol and dichloromethane) on the mitochondrial membrane. This mechanism may also have been responsible for the multiorganic alterations toxicity. Treatment with antianxiety drugs and selective serotonin uptake inhibitors was begun and the patient was discharged. *Conclusion:* The abuse of volatile substances such as isopropanol and, above all, dichloromethane, is associated with neuropsychological, cardiac, respiratory, hepatic and renal anomalies. There was mitochondrial dysfunction, which may have been the cause of the pathopysiology of these changes.

217. Inadvertant Administration of Concentrated Phenol for Obturator Nerve Blockade

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Objective: Phenol solutions between 5 to 7% have been used to produce obturator neurolysis in the management of adductor hip muscle spasticity. At high concentrations, phenol is a caustic liquid that is well absorbed through the skin and mucous membranes. Toxic effects following topical administration of phenol-containing products have been reported. We report a case of inadvertent administration of 90% phenol during an obturator nerve block procedure that resulted in local necrosis but no systemic toxicity. Symptoms resolved with supportive care. *Case Report:* A 53 year-old woman with a history of spinal cord injury underwent obturator nerve blockade with phenol to treat excessive muscle tone in her legs. Instead of receiving 6% phenol, she received one 1-mL injection in each obturator nerve (a total of 1.8 gm phenol). When the error was noted, she was admitted to the hospital for observation. Her hospital course was remarkable only for mild rhabdomyolysis (creatine phosphokinase 900 U/L) and hypokalemia (potassium 3.2 meq/L). The skin around the injection sites appeared dusky with superficial necrosis. She had no seizures, arrhythmias, or evidence of hepatitis, and was discharged after 2 days. Subsequent follow up showed resolving rhabdomyolysis (creatine phophokinase 200 U/L, 7 days post injection) and good wound healing around the injection sites. *Conclusions:* Phenol is a protoplasmic toxin, causing protein denaturation and coagulation necrosis. Dermal application has resulted in local burns and systemic toxicity has resulted in dysrhythmias, seizures and hepatic injury. In this patient, deep injection caused local necrosis but surprisingly, no serious systemic toxicity. *Reference:* Wax, PM. Antiseptics, Disinfectants, and Sterilants in Goldfrank LR, Flomenbaum NE, Lewin NA, et al (eds): Goldfrank's Toxicologic Emergencies, 7th ed., New York, McGraw Hill, 2002, p. 1283.

218. Severe Lactic Acidosis Caused by Sodium Nitroprusside in a Newborn with Congenital Heart Disease

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Objective: Sodium nitroprusside (SNP) is an antihypertensive drug used frequently in the critical care setting. Coadminstration of the antidote sodium thiosulfate usually prevents increases in cyanide concentrations during anesthesia or long-term SNP infusion (1). We report on a newborn with congenital heart disease which developed severe lactic acidosis due to the administration of SNP despite concomitant medication with sodium thiosulfate. *Case Report:* A 3800 g-female newborn was admitted to our hospital because of complex congenital heart disease (double inlet left ventricle, dysplasia of the right ventricle, atrial and ventricular septal defects with right ventricular outlet, transposition of the great arteries, hypoplastic ascending aorta). Due to the presence of hypoplastic ascending aorta treatment consisted of the administration of prostaglandin E1 to allow for adequate systemic perfusion via the patent ductus arteriosus. Because of a mismatch between pulmonary and systemic blood flow continuous treatment with SNP was started to shift perfusion from the pulmonary bed to the systemic circulation by reducing the afterload. To avoid iatrogenic intoxication with cyanide the patient received concomitant medication with sodium thiosulfate (ratio SNP/sodium thiosulfate of 1:10). On day 6 of SNP medication the patient developed profound lactic acidosis (ph: 7,26, pO_2 48,5 mm Hg, pCO_2 21,3 mm Hg, lactate 19 mmol/l, base excess −16,4 mmol/l). SNP was stopped; the patient was intubated and ventilated with FiO_2 100%. Due to rapid resolution of lactic acidosis no specific antidote (dimethylaminophenol—DMAP) was given; a substantial increase in the difference of arterio-venous oxygen saturation was also seen. Toxicological analysis which was done 24 h after the development of lactic acidosis still showed elevated levels of thiocyanate (41 mg/l; therapeutic <30 mg/l). *Conclusion:* Despite concomitant administration of sodium thiosulfate SNP may cause severe lactic acidosis due to the accumulation of cyanide with consecutive inactivation of cytochrome oxidase a-3 and blockade of cellular aerobic metabolism. The prolonged administration of SNP may have affected the detoxification capacity of the enzyme rhodanese which converts cyanide and thiosulfate into thiocyanate. Furthermore, rhodanese is predominantly located at a mitochondrial site, while thiosulfate—due to low lipophilicity—has limited intracellular distribution (2). This inequity in distribution in conjunction with prolonged SNP medication may have caused severe cyanide intoxication in our patient. *References:* 1. Hall VA, Guest JM. Sodium nitroprusside-induced cyanide intoxication and prevention with sodium thiosulfate prophylaxis. *Am J Crit Care* 1992; 1:19–25. 2. Baskin SI, Porter DW, Rockwood GA, et al. In vitro and in vivo comparison of sulphur donors as antidotes to acute cyanide intoxication. *J Appl Toxicol* 1999; 19:173–183.

219. Increasing Sirolimus Levels in a Multiorgan Transplant Patient Related to Interaction with Ciprofloxacin

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Objective: To describe a CYP3A4 interaction between sirolimus and ciprofloxacin. *Case Report:* A 5-year-old male was admitted for gastrointestinal bleeding. His past medical history included microvillus inclusion disease status post small bowel, liver, and pancreas transplant; gastrostomy tube, ileostomy, and indwelling catheter with multiple line infections; GI bleeding; hearing loss; and chronic neuropathic pain. Meropenem was started on hospital day (HD) 11, and ciprofloxacin on HD 13 for treatment of a Serratia line infection. After introduction of ciprofloxacin, he experienced a sudden and persistent increase in his sirolimus levels to above therapeutic range (goal 10 ng/ml), despite decreases in dosing. Simultaneously, his serum phosphate declined to a nadir of 1.7 mg/dl (0.55 mmol/L) despite increasing supplementation. Toxicology was consulted on HD 19. His physical exam and laboratory parameters otherwise remained unchanged from baseline. Sirolimus levels decreased after ciprofloxacin withdrawal on HD 19 and eventually normalized, as did serum phosphate concentrations. At parental request, sirolimus therapy was replaced with tacrolimus, which the patient was taking upon discharge. Instructions were given to monitor for potential interactions with tacrolimus. *Conclusion:* Sirolimus forms a complex to inhibit mammalian-Target of Rapamycin (m-TOR) and subsequent lymphocyte proliferation (1). It is not labeled for use either in the pediatric population or in liver transplantation. It is well established that the P450 isoenzyme CYP3A4 metabolizes sirolimus while ciprofloxacin is known to inhibit CYP3A4 (2,3). This inhibition may increase sirolimus levels. A literature review reveals no previously reported interaction between these drugs. The sirolimus levels did not decrease despite dosage reduction in this setting because of a 57–63 hour half-life, which in this case likely was prolonged further. The recent addition of ciprofloxacin prolonged this half-life through CYP3A4 inhibition. None of his other medications were known CYP 3A4 inhibitors. Hypophosphatemia is a known side effect of sirolimus administration (approximate incidence 7%) although its mechanism is unknown (4). Hypophosphatemia can cause encephalopathy, cardiac failure, rhabdomyolysis, and hemolysis. Toxic effects of sirolimus include pulmonary fibrosis, alveolar hemorrhage, anemia, leucopenia, and hyperlipidemia (1,4). We recommend careful monitoring of renal, pulmonary, hematologic, and metabolic parameters when sirolimus is administered with P450 inducers or inhibitors. *References:* 1. Wyeth. Rapamune (sirolimus) prescribing information. Vol. 2004. Philadelphia, PA, 2004. 2. Al-Bekairi A. Sirolimus. Drugdex. Vol. 2004. Vol. 122 ed: Thomson Micromedex, 2004. 3. Colaluca DM TT, Yeh TL. Ciprofloxacin. Drugdex. Vol. 122: Thomson Micromedex, 2004. 4. Pham PT, Pham PP, Danovitch GM, et al. Sirolimus-associated pulmonary toxicity. *Transplantation* 2004; 77:1215–1220.

220. Benzydamine and Tetrydamine Overdoses. Route Error of a Vaginal Douche

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Objective: Medication errors have been recognized as an important aetiology of toxic exposures. Benzydamine and tetridamine are nonsteroidal antiinflammatory agents used as vaginal lavage for non-specific vaginitis and as a co-adjuvant in moderate and severe vaginitis. In spite of their availability, data on overdoses are scarce or lacking. In the Spanish Poison Control Centre (SPCC), we have received a high number of consults due to the ingestion of these vaginal preparations. We decided, therefore, to review them in order to describe the toxicology and propose preventative measures. *Methods:* We retrospectively analysed all human exposures to antiinflammatory vaginal preparations available in Spain (benzydamine and tetridamine) reported to our service from January 1991 to December 2003. Data investigated included the caller's details, patient's age, gender, amount ingested and preparation, and clinical manifestations. *Results:* The number of cases meeting the inclusion criteria was 801. 90.4% were due to benzydamine and 9.6% to tetridamine. Of the patients, 86.4% were over 15 years old, 9.7% were older than 2 and the rest less than 2 years old. Gender was not a factor of exposure in children (49% were male in patients less than 14 years old). On the contrary, 84.7% of cases older than 14 years were female. In 73.2% of cases, benzydamine and tetridamine were ingested when they were mistaken for an oral preparation either in water solution or as a powder. The rest were suicidal attempts (0.6%) or unintentional misuse, when children or adults drank the preparation in error (26.2%). 31% of the patients were symptomatic at the time of the consult. Clinical features were mainly gastrointestinal (121 patients) followed by neurological (74) or both (51). The most common symptom was vomiting (74 cases), followed by dizziness (45), abdominal pain (57), nausea (42), pirosis and dysphagia (27 patients each). In the case of benzydamine, outstanding features were the presence of hallucinations, mainly visual, and agitation (33 and 20 patients, respectively). Severe cases included coma caused by tetridamine, and convulsions caused by benzydamine. Clinical features did not differ between children and adults. *Conclusion:* This is so far the largest report of benzydamine and tetridamine overdoses. Exposures were most commonly reported among female adults due to an error of the administration route. In spite of an alert to the companies and a change in the labelling seven years ago, intoxications are still very common. An effort should be made to encourage physicians and pharmacists to clearly explain the correct directions for use of these products.

221. Botulism: It is Still Not Easy to Diagnose at the Beginning of the Twenty First Century

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Introduction: Botulism is rare in Italy. Numerous cases may go unrecognised, especially when the course is mild, rapidly lethal or when the presentation of symptoms in the first few hours is not usual. We present 3 case-reports observed in our province in the last 12 months with the description of their particular clinical history. *Case Report 1:* A 34-year-old man arrived in the emergency department of our hospital with tremors, spasm of facial muscles and dysarthria after starting treatment with metoclopramide 24 hours previously for dizziness, vomiting and headache. After an initial diagnosis of extrapyramidal syndrome was made and treated with partial success with delorazepam, an unexpected respiratory arrest occurred and the patient was promptly intubated and ventilated. CT brain scan and CT angiography were both negative. Laboratory and toxicological analysis showed only a mild elevation of CPK (895 U/L) and of myoglobin (181 ng/mL). After a few hours in ICU sedation and paralysis were discontinued. The patient subsequently became alert and was able to partially move his hands and feet. In the same time fixed mydriasis was observed and the hypothesis of botulism emerged. Botulinum type A toxin was identified in faeces, blood and, subsequently, a few black olives found at the patient's home. Botulin ABE antiserum was administered to the patient. The patient was transferred from the ICU to a rehabilitation unit six months after the admission and the complete resolution was observed after ten months. *Case Report 2:* A 30-year-old male heroin abuser was admitted in hospital with diplopia, ptosis, unequal pupils, respiratory failure and generalised muscle weakness, but with partially conserved movements of his hands and feet. Myasthenia gravis and Guillain-Barré were excluded. After three days, when all other laboratory tests were negative, wound botulism was suspected since cellulitis was visible at the usual injection sites in his calves. Botulinum ABE antiserum was administered with clinical improvement but botulinum toxin was not formally identified. The patient was discharged from the hospital three months after admission. *Case Report 3:* A 24-year-old healthy man, arrived at the hospital with ophthalmoplegia, ptosis and dysphagia after starting metoclopramide treatment for vomiting two days earlier. Two hours later, when the patient was admitted in the ICU, the intensivist found that the father of the patient had been admitted to another hospital two days before for vomiting and had died the same day with a diagnosis of cerebral ischaemia. A diagnosis of botulism was suspected and the patient was immediately treated with the botulinum ABE antiserum. There was complete resolution of all his symptoms within one week. High levels of botulinum toxins type B and E were found in the father's blood during post mortem examination and also in the faeces of the son. *Conclusion:* Botulism can be difficult to diagnose and should be considered in patients presenting with unusual neurological signs and respiratory muscle weakness, particularly in the presence of partially preserved movements of the hands and feet. Suspected botulism must be ruled out with the correct laboratory test and, in the meantime, the administration of the antiserum must not be delayed.

222. Outcome of Pregnancy Following Maternal Treatment with Nicotine Replacement Therapy or Bupropion

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Objective: Smoking during pregnancy is an addiction that is harmful to the mother and her developing baby. Although smoking cessation is encouraged via support and counselling, some women also require pharmacological aids to achieve this (1,2). The objective of this prospective case series was to assess potential fetotoxicity following the use of nicotine replacement therapy (NRT) or bupropion during pregnancy. *Method:* Using standardised procedures, NTIS has provided prospective fetal risk assessment and collected outcome data on 22 pregnancies exposed to NRT patches (11) or bupropion (11). *Results:* The results are shown in Table 1. NRT: The majority (10/11) of liveborn babies were normal (91%). One baby had a haemangioma on the left cheek. Eight of the mothers also took other therapeutic drugs. Neither of the preterm infants was small for their gestational age, despite being subject to high levels of nicotine from patch and cigarette use. None of the 10 term babies were small for gestational age. The duration of use ranged from 1 to 18 weeks. Bupropion: Nine healthy term babies were delivered with no malformations. There was 1 miscarriage and 1 elective termination of pregnancy (ETOP) for unspecified reasons. Ten women were on monotherapy and the duration of treatment was 2 to 6 weeks. One infant was small for dates. *Conclusions:* The majority (NRT 91%; bupropion 100%) of liveborn babies were normal. One baby exposed to NRT had a haemangioma on her left cheek which is a very common anomaly of unknown aetiology. The incidences of miscarriage (1 per group, 9% vs. 10–20%) and ETOPs (1 bupropion, 9% vs. 23%) were within the expected range. There was no evidence of growth retardation with NRT use

TABLE 1
Outcome of pregnancy following maternal treatment with NRT patches or bupropion

Exposures (n)	Liveborn normal	Liveborn malformation	Miscarriages	Elective termination
NRT (11)	10[#]	1*	1	0
Bupropion (11)	9	0	1	1

[#]1 Premature (34/40) with severe hyaline membrane disease and jaundice, 1 premature (33/40) both mothers resumed smoking during pregnancy.
*1 Haemangioma left cheek.

in this study. However, the small numbers preclude the drawing of reliable conclusions. Overall, the results of this small series are consistent with those of other published data in pregnancy (3,4). Further research is required to enable an accurate assessment of the risk benefit ratio of using NRT and bupropion against the known risks of continued smoking. *References:* 1. McElhatton PR, et al. *Pharm J* 2000; 265:863–865. 2. Oncken CA, Kranzler HR. *Drug Alcohol Rev* 2003; 22:191–202. 3. Bupropion Pregnancy Registry Interim Report. 31st August 2003. 4. Molyneux A. *BMJ* 2004; 238:454–456.

223. Fetal Outcome Following Maternal Exposure to Emergency Contraceptives

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Objective: Hormonal contraceptives are normally contraindicated in pregnancy. In the UK an emergency contraceptive pill (ECP), PC4 has been on the market for many years (1). Recently a new ECP, levonorgestrel, (Levonelle 2) which can be used up to 72 hours post intercourse has been made available without prescription. If ECP failure occurs this may result in a greater number of pregnancies being inadvertently exposed to a contraceptive hormones in the early stages of pregnancy. This on-going prospective case series aims to collect data and assess the potential fetotoxic effects of inadvertent exposure to such hormones during pregnancy. *Method:* Using standardised procedures, NTIS has provided prospective fetal risk assessment in 32 pregnancies and collected outcome data in 20 that were inadvertently exposed to ECPs (10 Levonelle 2; 10 PC4). The remaining pregnancies are still in progress. *Results:* Pregnancy outcomes are shown in Table 1. All of the liveborn babies were normal. The incidence of miscarriage (2/10; 1/10) and elective terminations (1/10; 3/10) is within the expected range (10–20% and 23%, respectively). There was one intrauterine death (IUD) associated with a cystic hygroma following exposure to levonelle 2, but no causal relationship could be established. *Conclusions:* The preliminary data are encouraging. No congenital malformations in liveborn babies have been reported to date. There was one malformation in a fetus that died in utero. However, the small numbers preclude the drawing of reliable conclusions at the moment. Continued monitoring of all inadvertent ECP exposures in pregnancy is required to enable accurate fetal risk assessment. *Reference:* Scialli AR, et al. Drugs During Pregnancy and Lactation. Ed. Schaefer C. Elsevier 2001.

TABLE 1
Outcome of pregnancy following maternal exposure to emergency hormonal contraception

Maternal exposures	Liveborn normal (%)	Liveborn malformation	Miscarriages (%)	Elective termination (%)	IUD
All emergency contraception	12 (100)	0	3	4	1˜
Levonelle 2	6 (100)	0	2 (20)	1 (10)	1˜
PC4	6 (100)	0	1 (10)	3 (30)	0

˜IUD due to cystic hygroma, Levonelle 2 at 24 h post coitus.

224. Severe Coma and Focal Neurological Symptoms in a Large Intentional Oral Olanzapine Overdose: A Case Report

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Case Report: We report a case of a life-threatening overdose of olanzapine. A 36 year-old woman with a known psychiatric history, was found unconscious at home and admitted to the emergency department. She was comatose and a Glasgow Coma Score of <8 lead to acute intubation and transfer to the ICU. The patient showed clinical signs of aspiration. Current medications included olanzapine 30 mg daily and clonazepam 1 mg nightly. 3 empty olanzapine packets prescribed on the admission date were found, each containing 56×10 mg tablets, equivalent to an ingestion of approximately 1500 mg, which to our knowledge has not been previously reported. An additional possible ingestion of 100 mg of clonazepam was later revealed through patient history, once she regained consciousness. On arrival she was found tachycardic, with a SR of 129, blood pressure of 100/40 and a temperature of 38.9°C. She had rigid, tremulous extremities, normal pupil sizes, but one pupil was irregularly shaped, reacting sluggishly to light. There was urinary retention with a volume of 2000 ml and bilaterally positive Babinski's sign, which led to an acute CT scan and lumbar puncture, both normal. Arterial puncture showed mild compensated metabolic acidosis, blood glucose was elevated at 10.5 mmol/L, and there was significant leucocytosis. An initial drugscreen testing for benzodiazepines, tricyclic antidepressants, cyclic antidepressants, ethanol, lithium, paracetamol and salicylates was negative. Olanzapine was not tested for. She was intubated for 21 hours but did not produce any other symptoms (specifically no prolonged QT/QRS) apart from fever treated with antibiotics (a chest X-ray showed mild signs of aspiration pneumonia). After extubation she was on cardiac monitoring for an additional 24 hours, before being transferred in her habitual state for psychiatric treatment. Her positive neurological finds and leucocytosis resolved spontaneously. *Conclusion:* Olanzapine is still a relatively new antipsychotic and knowledge of clinical presentations and outcomes in overdose situations is limited. We report a case of a historically strongly confirmed overdose of approximately 1500 mg. This patient presented with deep coma, extrapyramidal symptoms, bilaterally positive Babinski's sign and leucocytosis, but produced no cardiac abnormalities. She was discharged to the psychiatric department 48 hours after admission with no sequelae. Olanzapine must still be considered a relatively safe drug in overdose situations, compared with traditional antipsychotics.

225. Profound Hypothermia in a Poisoning with Metformin and Tramadol

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Background: Lactic acidosis is a common effect reported in cases of metformin treatment or overdose. In severe tramadol poisoning, respiratory depression, coma, seizures and hypotension are common. We report a fatal intoxication with tramadol and metformin. *Case Report:* A healthy 20-year-old woman was found unconscious by her family after ingestion of 60 cps of tramadol (3 to 12 gr), 175 cps of metformin (87 to 175 gr), acetaminophen 19 gr, glibenclamide 50 mg. The time of ingestion was unknown. The emergency team found her in coma Glasgow 3, blood pressure 90/60 mm Hg, SpO_2 74% with respiratory breaks, glycemia 2 gr/l. Despite ventilatory support, volume expansion, epinephrine administration and external warming, the patient developed, at H4 after admission, hypothermia 27°C, bradycardia HR 35/mn, severe hypotension, severe lactic acidosis (pH 6.77, bicarbonates 4 mEq/l, lactates 14 mmol/l), hypokaliemia 2.5 mmol/l, decrease of coagulation factors. Glycemia did not fall under 0.69 gr/l. The evolution was marked by the persistence of bradycardia, profound lactic acidosis despite alkalinisation (max lactates 42 mmol/l), shock, moderate hepatic cytolysis, anemia and thrombopenia. Despite intensive care with administration of N-acetylcysteine, vasoactive drugs, CVVHDF for acidosis and hypokaliemia and CEC of warming up for hypothermia, the patient never recovered from the shock state and died at H20. Toxicological blood analyses at admission showed a concentration of 242 mg/l of acetaminophen and 4.67 mg/l of tramadol (TR: 01–0.3 mg/l): unfortunately, metformin assay was not available but plasma metformin level or lactates level do not have a prognostic significance. *Discussion:* Profound hypothermia has rarely been described with metformin, and never described with tramadol. The severe hypotension and probably the death were due to hemodynamic consequences of lactic acidosis and to the cardiovascular effects of tramadol. The mechanism of the profound hypokaliemia remained unclear and has not been described with any of the drugs ingested.

226. Do Contributors to the Journal of Toxicology Clinical Toxicology Accept the Position Statements on Gut Decontamination?

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Objective: To investigate whether physicians publishing in the Journal of Toxicology Clinical Toxicology are following the guidelines of the Position Statements when managing poisoned patients. *Method:* The Journal of Toxicology Clinical Toxicology, [Volumes 36 (1998) to 41 (2003)] was scanned for case reports mentioning gut decontamination (both papers in the journal and abstracts of papers and posters presented at 5 EAPCCT and 6 AAPCCT meetings). Only one report of each case was included. *Results:* 246 case reports were found of which 159 (64.6%) came from the US with the remainder from 22 other countries. Time to gut decontamination was seldom mentioned but the time of arrival of medical help or arrival at hospital was mentioned in 163 of the 237 cases for which gut decontamination was carried out and could be taken as a minimum time to gut decontamination. Only 22 (13.5%) of these patients were said to have reached medical help less than 1 hour after the overdose. One of these received no gut decontamination, 11 gastric lavage+activated charcoal, one gastric lavage alone, 8 activated charcoal (one with cathartic) and one activated charcoal with WBI. A further 45 (27.6%) presented at 1 to <2 hours, 47 (28.8%) at 2 to <4 hours and 48 (30.9%) at 4 hours or more after the overdose. In one case the time range was 3–5 hours. The greatest time to gut decontamination was 18 days. Nine reports (3.7%) mentioned that no gut decontamination was carried out (20 minutes to 3 days). Gastric lavage/aspiration was carried out in 109 (44.3%) cases (30 minutes to 20 days). Activated charcoal was given in 190 (77.2%) cases (time range <15 mins to 5 days). Whole bowel irrigation was carried out in 31 (12.6%) cases (time range 1 hour to 5 days). Ipecac was only mentioned once, and was followed by GL+AC. Other methods of decontamination mentioned were Fuller's earth (+GL+AC; diquat; death); cupric sulfate (diazepam; death); GL with KMnO4 (+AC+$MgSO_4$; strychnine); oral propylene glycol (cocaine body packer); 24 h gastric irrigation with sodium bicarbonate (+WBI; arsenic trioxide); emesis (unspecified; +MDAC; psylocibin); digital emesis (+AC; citalopram). In 120 (48.7%) cases more than 1 method of gut decontamination was used. MDAC was used in 20 cases but only 3 in agreement with the Position Statements. 27 patients (11.0%) died despite, in some cases, intensive gut decontamination. *Conclusions:* Few patients arrive in time to receive gut decontamination within 1 hour. Physicians continue to carry out gut decontamination well after 1 hour and often use more than one method.

227. A Review of the Overdose Section in the Drug Monographs of the Norwegian Pharmaceutical Product Compendium, Felleskatalogen

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Objective: Health care professionals contacting the Poison Information (PI) in Norway for advice on overdose, often refers to information concerning overdose and treatment in the drug monographs in the Norwegian Pharmaceutical Product Compendium, Felleskatalogen (FK). The FK is the most frequently used source to obtain information regarding the use of drugs and drug overdose and is distributed to health care professionals in Norway. The compendium is edited by representatives of the pharmaceutical industry. The information is based on the SPCs (Summary of Product Characteristics) and is usually in a condensed form. The information concerning overdose and treatment does not always seem to be consistent with the knowledge of the PI. The PI therefore wanted to find out if this information could be misleading and how common this problem is. *Methodology:* During 2002–2003 the PI did a systematic and critical review of the information in the overdose section for each drug monograph in FK 2002. A total of 1273 drug monographs were evaluated. The overdose information obtained for the individual drugs in the FK was compared with information in Poisindex database, FASS (The Swedish Pharmaceutical Product Compendium) and with our general experience and case reports submitted to the PI. The overdose sections were classified in four different categories (no information stated, acceptable information, inappropriate information and wrong/misleading information) according to evaluation of the quality of the information. *Results:* Table 1 shows how the drug monographs were classified. *Conclusion:* From a clinical toxicology point of view, the overdose information in the drug monographs had variable quality. Due to collaborative efforts between the governmental Norwegian Medicines Agency (SLV), the editors of the FK and the PI, steps have been taken to change the sections we evaluated to contain wrong or misleading information. However, obtaining satisfactory quality of the monographs is a demanding and time consuming process and needs continuing efforts from the pharmaceutical industry and the regulatory authorities. To improve the quality of the overdose information, poison

TABLE 1
Number of drug monograph in each category

No information stated	Acceptable information	Inappropriate information (some improvements recommended)	Wrong/misleading information	Total
505 (40%)	518 (40%)	240 (19%)	10 (0,8%)	1273 (100 %)

information centres and clinical toxicologists should be more involved, for example to compile comprehensive overviews of overdose.

228. Poisoning After Ingestion of Clonidine Eye Drops in Children

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Objective: Clonidine containing ophthalmic preparations are used for all forms of glaucoma and ocular hypertension in Germany. The concentration ranges from 0.625 to 2.5 mg per mL. To estimate the toxic risk after ingestion of clonidine eye drops in children we reviewed our poisoning cases. *Case Series:* From 1998 to 2003 we recorded 6 cases of poisoning in children (11 months to 3.5 years old). In most cases the ingestion was suspected firstly several hours later and the ingested dose was unknown. Typically parents or nurses noted somnolence or temulence (1 hour at the earliest) at unusual time of day. Somnolence progressed to deep sleep with tachycardia or bradycardia (4/6), hypotension (4/6), respiratory depression (3/6), miosis (1/6), and hypothermia (2/6). Symptoms disappeared in all cases under supportive treatment within 10 to 20 hours. Despite severe clinical feature neither sequelae nor fatality occurred. *Case Report:* A 2-year-old female with learning difficulties (8 kg body weight) presented to the emergency room with respiratory depression, hypotension (60/36 mm Hg), bradycardia (60 to 75 beats/min), hypothermia, and miosis 6 to 7 hours postingestion. She was fallen in deep sleep 45 min postingestion of eye drops. The parents missed maximum 1 ml eye drops containing 0.125% clonidine, equivalent to 1.25 mg and 156 micrograms/kg, respectively. Clonidine serum level was still in the toxic range (3.3 micrograms/L) 7 hours postingestion. In respect of this concentration the ingested dose was probably only about 0.1 ml corresponding to 100 micrograms, respectively. The treatment was supportive. Intubation and artificial ventilation were not necessary. Sinus node arrhythmia disappeared in the mean time without intervention. At admission the patient presented with fluctuating level of consciousness between somnolence and agitation. In further course the patient was sleeping for 3 hours. Awakening was possible at any time. The patient was discharged healthy 3 days postingestion. *Conclusion:* Poisoning with clonidine eye drops in infants and toddlers occurs after ingestion of very small doses (50 to 100 microlitres). Doses above 10 micrograms/kg cause cardiovascular symptoms. Doses above 20 micrograms/kg can result in respiratory depression. Symptoms usually appear within 30 to 60 min after ingestion, but were sometimes ignored by minders. To prevent such severe unintentional ingestions it is necessary to inform parents adequately about save storage and early symptoms of clonidine poisoning. *Reference:* Erickson SJ, Duncan A. Clonidine poisoning—an emerging problem: epidemiology, clinical features, management and preventative strategies. *J Paediatr Child Health* 1998; 34:280–282.

229. Drospirenone—Ethinyl Estradiol Oral Contraceptive: Potential Risk After Ingestion in Children

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Introduction: Drospirenone is a new progestin spironolactone-analogue with antimineralcorticoid and potassium sparing diuretic activity. The amount of drospirenone in each pill is 3 mg comparable to a 25 mg dose of spironolactone, but drospirenone has a

longer half-life (30 hours) than spironolactone (1.4 hours) and spironolactone's active metabolite canrenone (18 hours). The therapeutic dose for spironolactone in children is 1–3/mg/kg/day up to a maximum dose of 200 mg/day. Following an intensive, and possibly misleading, advertising campaign (1) the increased use and availability of drospirenone—ethinyl estradiol oral contraceptive can pose a significant potential risk after ingestion of only 3 pills in children with a weight less than 15 Kg. Since the introduction of drospirenone into the Italian market this drug was involved in 11.5% of all contraceptive cases referred to the Bergamo Poison Center during the last two years. *Case Report 1:* A 4-year-old 20-kg male child was admitted to our hospital 30 minutes after the ingestion of 4 pills. The child was treated with activated charcoal (5 grams) and intravenous fluid and was observed for 24 hours. He remained asymptomatic. Blood pressure, urine output and serum potassium concentration remained within normal limits. *Case Report 2:* A 2-year-old 13-kg male with bladder-uretheral reflux was sent to a local hospital after ingestion of an unknown amount of pills. The child was treated with activated charcoal (3 grams) and observed for 24 hours. No adverse effects of drospirenone were observed. *Case Report 3:* A 3-year-old 16-kg male was sent to a local hospital after the ingestion of two pills. The child was treated with activated charcoal (3 grams) and observed for 24 hours, again with no observed adverse clinical effects. *Conclusions:* Drospirenone—ethinyl estradiol overdose in children, unlike other oral contraceptives, can potentially cause a large diuresis, hypotension and hyperkalaemia. None of these problems were encountered in our small case series, however all our patients were treated early with activated charcoal. A larger international case series would be helpful to determine the actual toxicity of this drug in overdose, and whether activated charcoal or fluid resuscitation are necessary in all cases of accidental overdose in children. *Reference:* 1. Anon. Yasmin advert withdrawn—why and how. *Drug Ther Bull* 2003; 41(3):17–18.

230. Nosocomial Infections in Clinic of Emergency and Clinical Toxicology and Pharmacology: A One Year Study

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Objective: To describe the epidemiology of nosocomial infections (NI) in the Clinic of Emergency and Clinical Toxicology and Pharmacology. *Methods:* Prospective incidence survey. Analysis of surveillance data on 1311 patients (47% with drug poisoning, 11% with pesticide poisoning, 10% with corrosive poisoning, 4% with gaseous poisoning, 3% with alcohol poisoning, while other poisonings were much rarer) with 4377 patients-days, collected between 1st January 2003 to 31st December 2003, from the Clinic of Emergency and Clinical Toxicology and Pharmacology, National Poison Control Center, Military Medical Academy, Belgrade, Serbia and Montenegro. The diagnosis of NI (pneumonia, bloodstream infection—BSI, urinary tract—UTI, others) was based on CDC criteria. *Results:* The incidence was 10.1 per 1000 patient days. 55.8% of patients with NI were admitted to the clinic because of drug poisoning, 25.6% because of pesticide poisoning, 11.6% because of corrosive poisoning, 4.6% because of alcohols poisoning and 2.4% because of fungi poisoning. Infections at three major sites represented 97.7% of all reported NI (pneumonia 50%, UTI 22.7% , BSI 22.7%, others 2.7%). 73% of episodes of nosocomial pneumonia were associated with mechanical ventilation, 60% of nosocomial BSI occurred in patients with a central line, and all nosocomial UTI occurred in catheterized patients. Microorganisms were isolated in 72.7% of all episodes of NI. *Staphylococcus aureus* (18%), *Pseudomonas aeruginosa* (14%), *Escherichia coli* (14%), and *Acinetobacter spp.* (12%) were frequently isolated microorganisms. In patient with pneumonia *Staphylococcus aureus* was the most frequently reported isolate (36.4%). In patients with UTIs, *Escherichia coli* (33.3%) was the most frequently reported isolate. *Conclusion:* Surveillance of NI in Clinic of Emergency and Clinical Toxicology and Pharmacology play an important part in assessment of strategies to prevent their development. A multidisciplinary approach to prevent NI in ICU involving the whole intensive care team, hospital epidemiologist, clinical microbiologist, and hospital management is essential if we are to succeed in preventing NI. *References:* 1. Edmond MB. National and Intrenational Surveillace Systems for nosocomial infections. In: Wenzel RP, editor. Prevention and control of nosocomial infections. Philadelphia: Lippincot Williams & Wilkins; 2003. p. 109–119. 2. Centers for Disease Control and Prevention. Monitoring hospital acquired infections to promote patient safety—Unated States, 1990–1999. *MMWR* 2000; 49:149–153. 3. Weber DJ, Raasch R, Rutala WA. Nosocomial infections in the ICU. *Chest* 1999; 115:34S–41S. 4. Richards MJ, Edwards JR, Culver DH, Gaynes RP, the National Nosocomial Infections Surveillance System. Nosocomila infections in combined medical-surgical intensive care units in the United States. *Infect Control Hosp Epidemiol* 2000; 21:510–515.

231. Serum Bicarbonate as a Predictor of Toxic Salicylate Levels

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Introduction: Early in the course of toxicity, salicylate (ASA) poisoning is often challenging to diagnose. Some clinicians have used normal serum bicarbonate (SB) levels to rule out ASA toxicity. We hypothesized that normal SB levels can be associated with toxic serum ASA levels. *Methods:* A retrospective chart review of all human exposure (HE) ASA cases called to a regional poison center over a 36 month time period was performed. Clinical data, demographics, first drawn serum ASA levels and corresponding SB levels were documented. *Results:* A total of 309 ASA HE cases were managed at a healthcare facility. Of those cases, 265 (86%) had both an initial ASA (mg/dL) and a SB (mmol/L) level drawn as noted in Table 1 below. Of the 195 patients with a SB of 20 or greater, 52.8% (103/195) had toxic (>30 mg/dL) ASA levels. *Conclusion:* In this retrospective chart review, toxic ASA levels were frequently seen at normal SB levels. Clinicians should not rely on a normal SB to rule-out elevated ASA levels.

TABLE 1

ASA level	0–10	11–20	21–30	31–40	41–50	51–60	61–70	71–80	>80
Total cases	29	43	32	32	67	30	13	11	8
Mean SB	22.9	23.6	21.8	21.3	20.8	19.3	20.3	19.8	15.5

232. Oxygen Transfer and Consumption Disorders Due to Acute Poisonings Caused by Depressants of the Central Nervous System Could be Restored by Succinate-Containing Drug in Patients

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Objective: Severe acute poisonings caused by the mixture of barbiturates, neuroleptics, and tricyclic antidepressants are common in Russia. Alcohol is co-ingested frequently in case of these poisonings. They are accompanied by hypoxic damage, which may contribute to mitochondrial dysfunction and energy deficiency. Cytoflavine (C) is a novel antioxidant; each 10 ml vial of it contains succinate (1 g), N-methylglucamine (1.65 g), riboflavine (0.02 g), nicotinamide (0.1 g) and inosine (0.2 g). The aim of the present study was to assess oxygen transfer and utilization disorders in patients poisoned by neurodepressants and to evaluate the influence of succinate-containing drug on these parameters. *Methods:* 60 patients (pts) were included into the controlled study. All of them were comatose and mechanically ventilated. 38 pts received C (0.15 ml/kg b.i.d. IV) in addition to intensive care program. Arterial and venous blood and expired air were assessed for O_2 and CO_2 content, pH and base excess. According to Fick's principle the parameters of oxygen transfer and consumption were calculated. The data are presented as means±SEM. *Results:* The pts had an increased dead space to tidal volume ratio of 0.57±0.03 (compared with normal values 0.32±0.04), and increased right to left shunt to 20±2% of cardiac output. Oxygen diffusion into the pulmonary capillaries remained decreased after 3–4 days in the control group but improved in the C group. The right to left shunt decreased to normal values by the 5th day (from 21±2 to 4±1%) in the C group. Nevertheless the control group had elevated left to right shunt (19–12%). C restored mean partial arterial oxygen pressure by the 4 day (from 66±2 to 95±2). In the control group it substantially decreased. Oxygen consumption and extraction parameters were decreased on day 1. By 3–4 days the oxygen consumption and extraction was restored in C group. In the control group oxygen consumption progressively decreased to 94±8 ml/min*m^2 (normal values 149±16). Oxygen extraction was also reduced to 16±1 ml/l in the control group (normal values 37.8±0.4). The pts who received C had shorter duration of coma and decreased incidence of complications. *Conclusion:* C restores oxygen transfer and utilization in severe poisonings caused by mixtures of depressants of the central nervous system. The mechanism includes succinate-dependent improvement of mitochondrial respiration. *References:* Kwong L, Sohal RS. Substrate and site specificity of hydrogen peroxide generation in mouse mitochondria. *Arch Biochem Biophys* 1998; 350:118–126. Sahlin K, Gorski J, Edstrom L. Influence of ATP turnover and metabolite changes on IMP formation and glycolysis in rat skeletal muscle. *Am J Physiol* 1990; 259:C409–C412.

233. Fatal Poisoning with Ibuprofen

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Objective: To describe the first lethal intoxication with ibuprofen registered by the Czech Toxicological Information Centre (TIC). Intoxications with ibuprofen belong to the most frequent intoxications in the inquiries of the TIC because of the availability of ibuprofen without a prescription. In the past three years TIC received a total of 1144 calls concerning ibuprofen overdose. *Case Report:* A 33-year-old woman ingested in the morning 36 grams of ibuprofen (507 mg/kg) as a suicidal gesture. Two hours later she was admitted to the hospital, at this time she had drowsiness, nausea, headache and tachycardia (100 beats/min). Gastric lavage did not reveal tablets and charcoal was given. Screening toxicology from urine was negative for tricyclic antidepressants, benzodiazepines, cocaine, opiates, barbiturates, methamphetamine/amphetamine, and tetrahydrocannabinol. Over two hours the patient developed coma, mydriasis, hypotension and respiratory failure, transient metabolic acidosis (lowest pH 6.952), hypernatraemia (highest 206 mmol/l), hyperglycaemia (highest 24.10 mmol/l) and hyperosmolality (highest 437 mOsm/l). Aspartate aminotranferase (AST) and alanine aminotransferase (ALT) were only mildly increased to 1.35 and 1.20 microkat/l (normal range AST 0.16–0.72 microkat/l and ALT 0.17–0.78 microkat/l). About 12 hours after ingestion she was transferred to the intensive care unit. She had a Glasgow coma scale of 3–4, and hypotension requiring treatment with norepinephrine. Electrolyte imbalance, especially hypernatraemia, was difficult to compensate. Serum creatinine and urea level increased in the following two days from 76 to 437 micromol/l and from 3.7 to 13.5 mmol/l, respectively. Circulatory instability was present. The patient was deeply comatose with signs of cerebral oedema, and died on day 4 due to circulatory failure. The medical history of the patient included fundoplication surgery of the stomach that might have prevented removal of tablets by emesis, but appeared otherwise insignificant. *Conclusion:* Ibuprofen overdose in adults only rarely results in significant toxicity (1–3). In toxicological literature, to our knowledge, only one lethal case has been reported in a 64-year-old man (1), who ingested 24 g of ibuprofen (407 mg/kg). In the calls to the Czech TIC the highest ingested dose was 60 g of ibuprofen (750 mg/kg) in a 26-year-old man. The treatment was only supportive and the patient recovered completely. *References:* 1. Hall AH, Smolinske SC, Kulig KW, Rumack BH. Ibuprofen overdose-a prospective study. *West J Med* 1988; 148(6):653–656. 2. Hall AH, Smolinske SC, Stover B. Ibuprofen overdose in adults. *J Toxicol Clin Toxicol* 1992; 30:23–37. 3. McElwee, NE, Veltri JC, Bradford DC, Rollins DE. A prospective-based study of acute ibuprofen overdose: complications are rare and routine serum levels not warranted. *Ann Emerg Med* 1990; 19(6):657–662. Acknowledgement: Supported by MSM 0021620807.

234. Outcome of Pregnancy Following Maternal Treatment with Retinoids

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Objective: Evidence from animal and human data indicate that exposure to systemic retinoids during pregnancy is associated with an increased risk of major congenital malformations (1,2). Fewer data are available on topical use. The objective of this

TABLE 1
Outcome of pregnancy following maternal treatment with retinoids

Exposures (n)	Liveborn normal	Liveborn malformation	Miscarriages	Elective termination
Isotretinoin (31)	9*	0	4	18
Isotretinoin+acitretin (1)	1	0	0	
Etretinate (1)	1	0	0	
Total systemic (33)	11	0	4	18
Topical isotretinoin (14)	9	1#	1	3

*Includes 2 sets of twins.
#Renal agenesis.

prospective case series is to assess potential fetotoxicity following treatment of pregnant women with either systemic or topical retinoids. *Method:* Using standardised procedures, NTIS has provided prospective fetal risk assessment and collected outcome data in 47 pregnancies exposed to therapeutic doses of retinoids. *Results:* The results are shown in Table 1. There were no congenital malformations among the 11 liveborn babies exposed to oral retinoids. Miscarriages occurred in 4 pregnancies (13% vs 10–20% expected) and elective terminations in 18 (58% vs. 23% expected). Of the 14 pregnancies exposed to topical isotretinoin, 1 baby had a malformation, renal agenesis (1/10, 10% vs. 2–3 expected), but the miscarriage rate (7% vs. 10–20%) and the termination rate (21% vs. 23%) were within the expected range. *Conclusions:* In this small case series the majority of liveborn babies were normal. There was one malformation in the topical exposure group but none in the oral exposure groups, which is slightly unusual. The termination rate in the oral exposure group was much higher than the background rate (58% vs 23%) probably due to the unacceptably high incidence of major malformations attributed to these drugs. There were no increases in the incidence of miscarriages in either exposure groups. However, the small numbers preclude the drawing of reliable conclusions. Further data are required before any firm conclusions can be drawn regarding the safety of topical retinoid use in pregnancy. *References:* 1. Collins, et al. *Ann Rev Pharmacol Toxicol* 1999; 39:399–430 2. Wanju, et al. *J Am Acad Dermatol* 1992; 26:599–606.