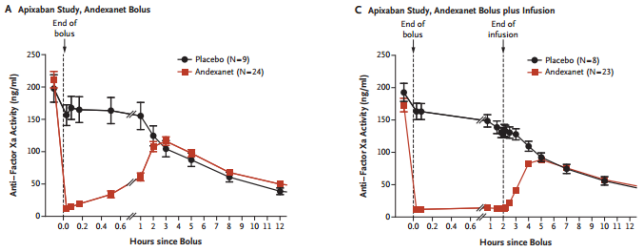
Slide 1	# Poisons and Poisoning Nick Holford Dept Pharmacology & Clinical Pharmacology University of Auckland, New Zealand	
Slide 2	# Poisons and Poisoning φαρμακον pharmakon Medicine Poison Magic Spell 	
Slide 3	# Objectives ➢ Learn some typical signs of acute drug poisoning ➢ Understand the pharmacological basis for enhancing elimination of drugs ➢ Understand the pharmacological basis for the use of specific antidotes 	Henretig FM, Kirk MA, McKay CA. Hazardous Chemical Emergencies and Poisonings. N Engl J Med. 2019;380(17):1638-55.

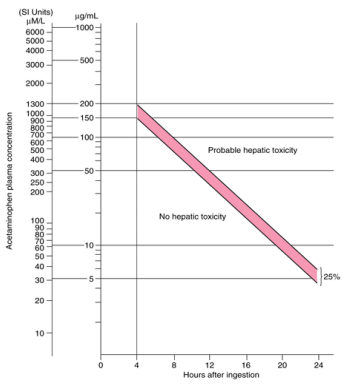
Slide 4	# Diagnosis ➢ History » Patients rarely lie » But may be unreliable – Sedation – Amnesic drug effects 	
Slide 5	# Diagnosis ➢ Pupils » Constricted – opiates (morphine) – clonidine – anti-cholinesterases (neostigmine) » Dilated – atropine – tricyclic antidepressants (amitriptyline) – amphetamine/MDMA (‘ecstasy’)/BZP (‘party pills’) 	MDMA 3,4-Methylenedioxymethamphetamine http://en.wikipedia.org/wiki/MDMA BZP benzylpiperazine http://en.wikipedia.org/wiki/Benzylpiperazine
Slide 6	# Diagnosis ➢ Skin » Sweating – Increased amphetamine – Decreased atropine » Bullae – carbon monoxide – [barbiturates] 	

Slide 7	**Diagnosis** ➢ Odour » ethanol » garlic – arsenic – organophosphates (anti-cholinesterase) » almonds – cyanide 	
Slide 8	**Diagnosis** ➢ Clinical Chemistry » Blood – salicylate – paracetamol – ethanol – carbon monoxide – tricyclics – digoxin – theophylline 	
Slide 9	**Diagnosis** ➢ Clinical Chemistry » Urine – salicylate – opioids – tricyclics 	

Slide 10	# Diagnosis ➢ ECG » Long PR – Calcium Channel – Verapamil » Wide QRS – Sodium Channel – Amitriptyline » Long QT – Potassium Channel – Amiodarone 	
Slide 11	# Treatment ➢ General Supportive » A Airway » B Breathing » C Circulation 	
Slide 12	# Decrease Absorption ➢ [emesis] » syrup of ipecac ➢ [gastric lavage] » must have reflexes » not for corrosives/hydrocarbons ➢ activated charcoal - IMPORTANT » 50g every 4 h ➢ Fuller's Earth (or activated charcoal) » paraquat (herbicide)  	Treatment of corrosive ingestion is reviewed here: Hoffman RS, Burns MM, Gosselin S. Ingestion of Caustic Substances. N Engl J Med. 2020;382(18):1739-48. http://en.wikipedia.org/wiki/Activated_charcoal http://en.wikipedia.org/wiki/Fuller's_earth Note that treatment of paraquat poisoning seems to be rarely effective. Gawarammana IB, Buckley NA. Medical management of paraquat ingestion. Br J Clin Pharmacol. 2011;72(5):745-57.

Slide 13	**Increase Elimination** ➢ Activated Charcoal » "enteral dialysis" ➢ Haemoperfusion » charcoal theophylline » ion exchange salicylate ➢ Haemodialysis » methanol (wood alcohol) » ethylene glycol (anti-freeze) ➢ [Diuresis] 	Note also fomepizole may be used to treat ethylene glycol and methanol poisoning (https://en.wikipedia.org/wiki/Fomepizole)
Slide 14	**Specific Antidotes** ➢ N-acetylcysteine » paracetamol ➢ Naloxone » morphine ➢ Flumazenil » benzodiazepines ➢ Ethanol » methanol ➢ Fomepizole » ethylene glycol, methanol 	https://en.wikipedia.org/wiki/Fomepizole Naloxone is licensed in NZ as a nasal spray https://nzf.org.nz/nzf_7017 . This formulation is intended for emergency use by non-health professionals but is currently only available on prescription. Naloxone is available in the USA for over the counter sale from pharmacies (Cohen et al 2020). Cohen BR, Mahoney KM, Baro E, Squire C, Beck M, Travis S, et al. FDA Initiative for Drug Facts Label for Over-the-Counter Naloxone. N Engl J Med. 2020;382(22):2129-36.
Slide 15	**Specific Antidotes** ➢ Chelation » desferrioxamine iron » edetate lead » penicillamine copper, mercury » hydroxocobalamin cyanide ➢ Atropine/pralidoxime » anti-cholinesterases ➢ Phytomenadione (vitamin K1) » Warfarin ➢ Protein Binding Agent » digoxin F(ab) digoxin » idarucizumab F(ab) dabigatran » andexanet apixaban, rivaroxaban 	Pollack CV, Reilly PA, Eikelboom J, Glund S, Verhamme P, Bernstein RA, et al. Idarucizumab for Dabigatran Reversal. N Engl J Med. 2015 DOI: 10.1056/NEJMoa1502000 Eddleston M, Chowdhury FR. Pharmacological treatment of organophosphorus insecticide poisoning: the old and the (possible) new. Br J Clin Pharmacol. 2015:doi:10.1111/bcp.12784. andexanet (not in NZF) Andexxa—an antidote for apixaban and rivaroxaban. JAMA. 2018;320(4):399-400. The reversal agent, PB2452 (not in NZF) is a monoclonal antibody fragment that binds ticagrelor (an anti-platelet agent) with high affinity; Bhatt DL, Pollack CV, Weitz JI, Jennings LK, Xu S, Arnold SE, et al. Antibody-Based Ticagrelor Reversal Agent in Healthy Volunteers. N Engl J Med. 2019;380(19):1825-33.

Slide 16	# Anti Factor Xa Activity  	Siegal DM, Curnutte JT, Connolly SJ, Lu G, Conley PB, Wiens BL, et al. Andexanet Alfa for the Reversal of Factor Xa Inhibitor Activity. N Engl J Med. 2015;doi:10.1056/NEJMoa1510991.
Slide 17	# Specific Antidote ➢ Paracetamol Hepatotoxicity » Minor metabolite is NAPQI (N- acetyl-p-benzoquinoneimine) – Formed by CYP2E1 – Ethanol induces CYP2E1 » NAPQI inactivated by glutathione » Liver damage caused by NAPQI » Glutathione reserves used up by large doses (> 15 grams of paracetamol) ➢ Acetylcysteine supplies SH to make more glutathione ➢ UK guidelines (2014) for treatment shown to be cost-ineffective 	“Paracetamol poisoning is the most common acute overdose seen in industrialized countries [1, 2]. It is estimated that between 82 000 and 90 000 patients present in the UK each year with paracetamol overdose [3–5]. Between 150 and 250 deaths occur annually, the vast majority in patients who have presented late, after a staggered overdose or after unintentional therapeutic excess [6–9]. Deaths or episodes of liver failure in patients [10] who present and are treated within 8 h of a single acute ingestion are extremely rare [1, 5, 11].” Bateman DN, Carroll R, Pettie J, Yamamoto T, Elamin MEMO, Peart L, et al. Effect of the UK's revised paracetamol poisoning management guidelines on admissions, adverse reactions and costs of treatment. Br J Clin Pharmacol. 2014;78(3):610-8. Ethanol can induce and “block” CYP2E1 at the same time. The "blocking" of metabolism of ethanol by itself is a manifestation of mixed-order saturable elimination as shown by the associated decrease in 'clearance' due to concentration dependent clearance.There are four processes involved in the paracetamol and ethanol interaction which are based on the same underlying mechanism of binding to CYP2E1. 1. Metabolism of ethanol by CYP2E1 2. Induction of CYP2E1 by ethanol 3. Metabolism of paracetamol by CYP2E1 4. Inhibition of paracetamol CYP2E1 metabolism by ethanol When ethanol binds to CYP2E1 it is metabolized and with continued ethanol binding the CYP2E1 protein is induced so that the

		enzyme becomes more active and metabolism is faster. When paracetamol binds to CYP2E1 it is metabolized to NAPQI. If ethanol is present and bound to CYP2E1 then paracetamol metabolism to NAPQI is reduced because of competition for the same binding site. The process of induction and de-induction is gradual with a protein turnover half-life of about 3 days so it takes about 2 weeks to induce and 2 weeks to de-induce. When ethanol binding is no longer present then the CYP2E1 protein decreases (de-induction) and enzyme activity returns to the uninduced state. If CYP2E1 has been induced and ethanol is stopped (and therefore not bound to CYP2E1) then paracetamol will be metabolized more quickly to NAPQI. As CYP2E1 becomes de-induced the metabolism of paracetamol will decrease until activity returns to the uninduced state. The risk of hepatotoxicity from paracetamol metabolism to NAPQI will be higher when CYP2E1 is induced and there is no ethanol present than the risk if ethanol is present. Thummel KE, Slattery JT, Ro H, Chien JY, Nelson SD, Lown KE, et al. Ethanol and production of the hepatotoxic metabolite of acetaminophen in healthy adults. Clin Pharmacol Ther. 2000;67(6):591-9. A “two bag” 12 h administration of acetylcysteine appears to be safer. Chiew AL, Isbister GK, Duffull SB, Buckley NA. Evidence for the changing regimens of acetylcysteine. Br J Clin Pharmacol. 2016;81(3):471-81.
Slide 18	N-Acetylcysteine Treatment Nomogram for Paracetamol Overdose in Adults  Children: 225 mg/L at 2 hours Anderson et al. 1999 [Auckland] 	http://www.merck.com/mmpe/sec21/ch326/ch326c.html Anderson BJ, Holford NH, Armishaw JC, Aicken R. Predicting concentrations in children presenting with acetaminophen overdose. J Pediatrics. 1999;135(3):290-5.

Slide 19	**Clinical Applications** ➢ Approach to Poisonings » ABC and General Support » Specific antidotes are uncommon ➢ Use physiology and pharmacology to assist in diagnosis ➢ Consider factors affecting drug clearance if enhanced elimination procedures are used 	
Slide 20	**Assessment Short Answer Question Examples** 1. Give an example of a physical sign of drug poisoning and a medicine causing this. 2. Explain how activated charcoal may enhance the elimination of drugs. 3. What specific antidote may be used to treat cyanide poisoning? 	Henretig FM, Kirk MA, McKay CA. Hazardous Chemical Emergencies and Poisonings. N Engl J Med. 2019;380(17):1638-55.