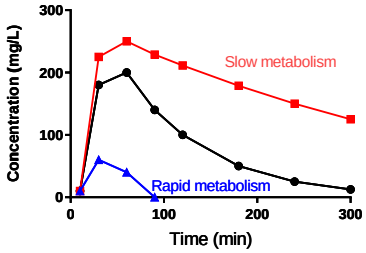
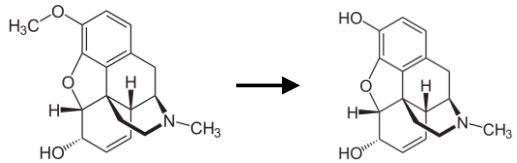
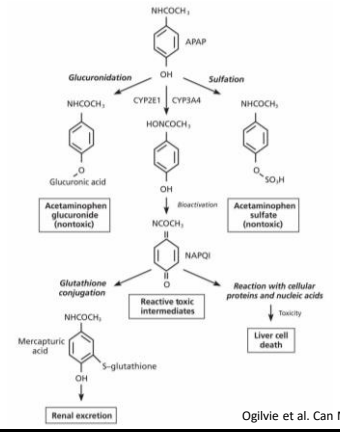
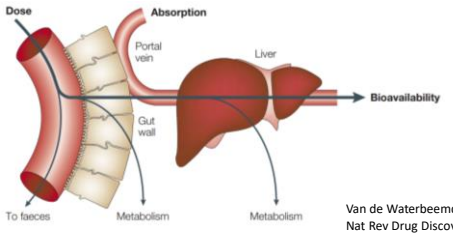
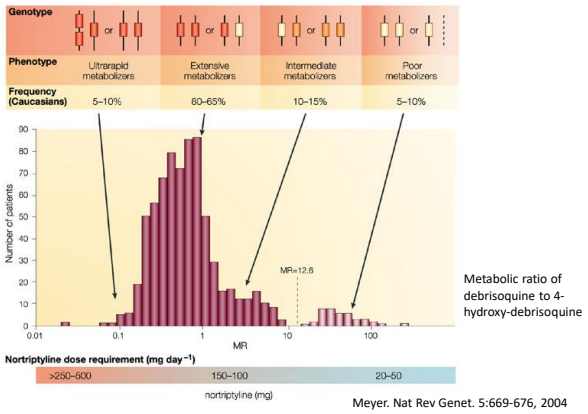
Slide 1	# Drug metabolism MBChB 221B Dr Stephen Jamieson Dept of Pharmacology and Clinical Pharmacology Auckland Cancer Society Research Centre	
Slide 2	## Learning objectives • Understand why drug metabolism is important • Learn the major drug metabolism reactions • Appreciate the potential role of drug metabolism in drug-drug interactions and toxicity • Learn the major CYP enzymes and at least one clinically relevant substrate for each	
Slide 3	## What is drug metabolism • Metabolism is the biotransformation of drugs – Enzyme-catalysed chemical change to the drug molecule; either building molecule up or breaking down • Biotransformation reactions typically generate more polar metabolites – Most drugs are lipophilic – Enhance excretion through urine or bile – Metabolites less likely to diffuse into cells	Most drugs are lipophilic and will not be renally excreted, as the fraction of drug that is filtered in the glomerulus will be reabsorbed back into the bloodstream. For elimination from the body, these drugs are generally metabolised into more polar metabolites that can then be excreted from the body in the urine (or the bile).

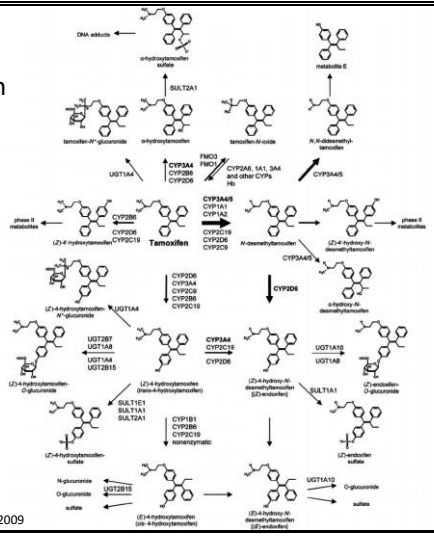
Slide 4	**Why is drug metabolism important** • Drug metabolism can directly influence the concentration-time profile in the body – Concentration determines effect  Source: Steve Jamieson	Drug metabolism directly influences drug concentrations in the body and therefore can influence the effect of the drug. Rapidly metabolised high extraction drugs will achieve lower plasma concentrations than slowly metabolised low extraction drugs.
Slide 5	**Why is drug metabolism important** • Drug metabolism can directly influence the concentration-time profile in the body – Concentration determines effect • Major route of drug elimination – Generally inactivates drugs • Can increase drug activity – Activation of prodrug (e.g. codeine to morphine)  Codeine Morphine Source: Wikimedia commons	In most cases, metabolism will reduce the activity of the drug. A major exception is prodrugs, which require metabolism for activation.
Slide 6	**Why is drug metabolism important** • Drug metabolism can directly influence the concentration-time profile in the body – Concentration determines effect • Major route of drug elimination – Generally inactivates drugs • Can increase drug activity – Activation of prodrug (e.g. codeine to morphine) • Production of toxic metabolites – e.g. paracetamol	Some drug metabolites may be toxic, e.g. paracetamol

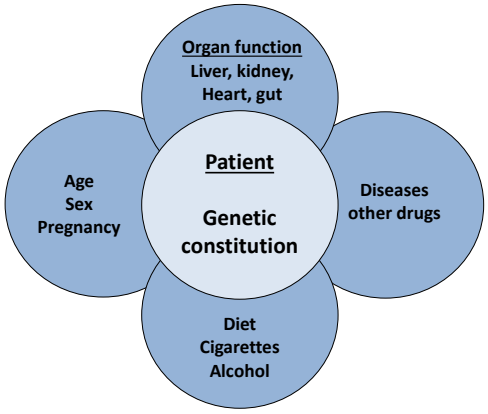
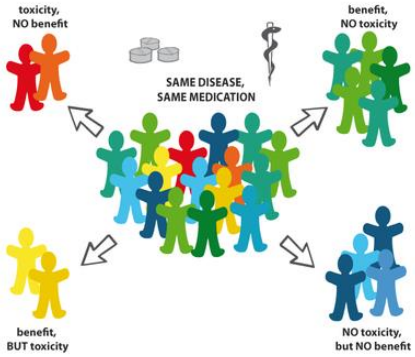
Slide 7	**Paracetamol metabolism**  Ogilvie et al. Can Med Assoc J. 184:1492-1496, 2012	Overdose of paracetamol can result in saturation of glutathione conjugation of a reactive metabolite, leading to buildup of the reactive metabolite, which can cause liver cell death.
Slide 8	**Why is drug metabolism important** • Drug metabolism can directly influence the concentration-time profile in the body – Concentration determines effect • Major route of drug elimination – Generally inactivates drugs • Can increase drug activity – Activation of prodrug (e.g. codeine to morphine) • Production of toxic metabolites – e.g. paracetamol • Can explain drug-drug interactions • Source of between patient variability	Drug metabolism can also be responsible for drug drug interactions and is a major source of inter-patient variability.
Slide 9	**Possible sites of drug metabolism** • Liver – Major site of drug metabolism – First pass metabolism of oral drugs (e.g. morphine) • May necessitate dosing by other routes • Intestinal wall – CYP450 enzymes  Van de Waterbeemd and Griffin. Nat Rev Drug Discov. 2: 192–204, 2003	The liver is the major site of drug metabolism. All orally administered drugs have to avoid first pass metabolism before they reach the systemic circulation and become bioavailable. Some oral drugs, e.g. simvastatin, can also be metabolised be enzymes present in the gut wall.

Slide 10	**Possible sites of drug metabolism** • Liver – Major site of drug metabolism – First pass metabolism of oral drugs (e.g. morphine) • May necessitate dosing by other routes • Intestinal wall – CYP450 enzymes • GI tract – Gut bacteria and proteases • Plasma – Esterases (prodrug activation) • Lungs – Metabolism of aerosol sprays	Microflora in the gut may encounter non-absorbed drug and metabolise it, assisting with absorption. Some drugs are administered as ester prodrugs to enhance their absorption. Esterases in the plasma can then metabolise the ester and release the active drug.
Slide 11	**Metabolism reactions** • Oxidation – Add oxygen atom through loss of electrons (H^+) – Typically catalysed by CYPs, FMO, oxidases and dehydrogenase enzymes • Reduction – Add H^+ with or without loss of oxygen atoms • Hydrolysis – Water molecule is added to compound, usually resulting in bond cleavage • Conjugation – Addition of endogenous substrate to increase molecular mass, polarity, water solubility – Glucuronidation, sulphation, acetylation, methylation, glutathionylation • A single drug may be metabolised by multiple routes and by multiple enzymes – Any enzyme can be a drug metabolising enzyme	Historically drug metabolism reactions have been referred to as phase I (e.g. oxidation, reduction, hydrolysis) and phase II (conjugation) reactions with phase I reactions involved in inactivating the drug and unmasking a molecule so that phase II reactions can occur and promote the excretion of the metabolite. Many textbooks still refer to metabolism reactions in this way. However, these terms are outdated. The so-called phase I reactions don't always inactivate drugs, while conjugation reactions don't always follow oxidation, reduction and hydrolysis reactions or necessarily enhance the excretion of the drug.
Slide 12	**Cytochrome P450 enzymes** • Superfamily of metabolising enzymes – 57 human CYP genes across >20 families – CYP families 1-3 are predominantly involved in drug metabolism • Most common drug metabolising enzymes – Catalyse oxidation reactions – 5 isoforms metabolise approx 90% of drugs • CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A4 • Most common reaction is a monooxygenase reaction – Requires O_2, NADPH and cytochrome P450 reductase Drug + O_2 + H^+ + NADPH → oxidised drug + H_2O + $NADP^+$	The most important oxidative enzymes are the CYP450 family. The CYPP450 enzyme system is responsible for the metabolism of over 50% of drugs used clinically. Often also called the 'microsomal mixed function oxidase' family. These are haem proteins that sit within liver cells, mostly associated with endoplasmic reticulum with a few associated with mitochondria. CYPs oxidise a large variety of drugs but also oxidise a number of endogenous substances, particularly steroid hormones, fatty acids and prostaglandins.

Slide 13	**CYP-mediated drug metabolism** • Some drugs inhibit CYPs and other drug-metabolising enzymes – Prevent the metabolism of itself or co-administered drugs • Increased toxicity • Reduced activation of prodrugs • The expression of some CYP enzymes can be upregulated by environmental factors or drugs – Enhance the metabolism of other drugs • Reduced activity • Increased levels of toxic metabolites • Function of CYP enzymes differs amongst individuals – Differences in gene expression – Genetic polymorphisms	The activity of drug metabolising CYP enzymes can be altered (inhibited or induced) by drugs or environmental factors, while variability in CYP function exists between individuals through differences in gene expression or genetic polymorphisms. Any change in CYP activity (through induction/inhibition or interindividual variability) can result in altered drug concentrations and potentially increased toxicity (if drug levels are increased) or reduced activity (if drug levels are decreased).
Slide 14	**Important CYP isoforms** • CYP1A2 – Clinically relevant substrates: theophylline, caffeine – Drug interactions: cimetidine (inhibition); tobacco, bbq meat, cruciferous veges (induction) • CYP2E1 – Clinically relevant substrates: ethanol, paracetamol – Drug interactions: chronic ethanol consumption increases CYP2E1 expression	An example of a CYP1A2 drug drug interaction is in patients who smoke being treated with theophylline. Smoking can induce CYP1A2 so greater doses of theophylline, a CYP1A2 substrate, are required to have the same effect as in non-smokers. This can be problematic if the patient stops smoking and the dose isn't adjusted (Kroon, Am J Health-Syst Pharm 64:1917-1921, 2007). For CYP2E1, high ethanol intake can induce CYP2E1 activity and promote metabolism of paracetamol to its toxic metabolite. Need very high doses of paracetamol before this becomes an issue.
Slide 15	**Important CYP isoforms** • CYP2D6 – Clinically relevant substrate: debrisoquine, tricyclic antidepressants (amitriptyline), codeine – Drug interaction: fluoxetine (inhibition) – Over 100 allelic variants	Genetic polymorphisms exist in CYP2D6 that have different phenotypes in their ability to metabolise drugs. This leads to inter-individual variability in drug concentrations and drug activity.

Slide 16	**CYP2D6 genetic polymorphism**  Metabolic ratio of debrisoquine to 4-hydroxy-debrisoquine Meyer. Nat Rev Genet. 5:669-676, 2004	Individuals with a genetic polymorphism in CYP2D6 that give a phenotype of "poor metabolisers" need a much lower dose of a CYP2D6 substrate to have the same effect as "ultrarapid metabolisers".
Slide 17	**Important CYP isoforms** • CYP2D6 – Clinically relevant substrates: debrisoquine, tricyclic antidepressants (amitriptyline), codeine – Drug interaction: fluoxetine (inhibition) – Over 100 allelic variants – Drug companies try to avoid compounds that are substrates for CYP2D6	Because of difficulties individualising patient dosing it is simplest to avoid drugs that are metabolised by CYP2D6.
Slide 18	**Important CYP isoforms** • CYP2C9 – Clinically relevant substrate: S-warfarin – Drug interactions: cimetidine inhibition of warfarin metabolism – Genetic polymorphisms alter ability of patients to metabolise warfarin • CYP2C19 – Clinically relevant substrates: omeprazole, clopidogrel – Drug interactions: omeprazole also inhibits CYP2C19 reducing metabolism of coadministered CYP2C19 substrates – Genetic polymorphisms • See Nuala Helsby lecture	Both drug drug interactions (CYP2C9: e.g. cimetidine and warfarin, CYP2C19: e.g. omeprazole and clopidogrel) and genetic polymorphisms can alter the activity of CYP2C9 and CYP2C19.

Slide 19	**Important CYP isoforms** • CYP3A4 – Major enzyme for ~ 30% of drugs currently on the market – Major enzyme in liver, intestines, also in kidney, lung, placenta and uterus – Clinically relevant substrates: erythromycin, simvastatin, felodipine – Genetic polymorphisms exist but don't lead to significant interindividual variability – Drug interaction: • Erythromycin, grapefruit juice (inhibition) • Rifampicin, St John's wort (induction)	CYP3A4: the most common drug metabolizing enzyme. Genetic polymorphisms are rare but drug drug interactions (e.g. grapefruit juice and the oral contraceptive pill) are common.
Slide 20	**Conjugation reactions** • Addition of endogenous substrate to drug or metabolite – Increases molecular mass, polarity, water solubility • Facilitates excretion through bile or urine – Typically terminates biological activity • Exception: Morphine-6-glucuronide is more active – Glucuronidation is a major pathway • Often follow on from a CYP-catalysed reaction but not all drugs require prior metabolism – (Outdated) concept of phase I & phase II reactions • Less prone to drug-drug interactions and genetic polymorphisms due to large capacity and overlapping substrate specificity	Enzyme induction/inhibition and genetic polymorphisms are much less common with conjugation reactions. These reactions have a large capacity, as the enzymes involved don't just catalyse the metabolism of drugs, but also many endogenous substances, so saturation is unlikely. Some drugs do inhibit conjugation enzymes, but in most cases this won't lead to drug drug interactions as multiple conjugation enzymes often catalyse the same reaction so if the activity of one enzyme is reduced (through inhibition or interindividual variability), another enzyme can metabolise the drug instead.
Slide 21	Tamoxifen biotransformation  Brauch et al. Clin Chem. 55:1770-1782, 2009	A single drug may be metabolised by multiple different enzymes, many of which can catalyse the same reaction (e.g. tamoxifen metabolism)

Slide 22	Factors influencing drug metabolism  Source: James Paxton	There is considerable interindividual variability in drug metabolism. Genetics (polymorphisms or mRNA expression of drug metabolising enzymes), age, gender, pregnancy, organ function, disease state and diet can all influence drug metabolism.
Slide 23	Variability in metabolism  Source: http://www.ukc.insel.ch	Variability in metabolism will lead to variability in drug activity for drugs with narrow therapeutic windows unless individualised doses are given. Rapid metabolisers will be more likely to have lower drug concentrations and may be at risk of no toxicity but no benefit, while poor metabolisers will achieve high concentrations so will be at risk of benefit but toxicity. To account for the variability in metabolism, therapeutic drug monitoring approaches can be used to ensure drug concentrations are within the therapeutic range for an individual and to maximum the chance of achieving benefit and no toxicity.
Slide 24	Revision questions • Explain the different effects that metabolism can have on the therapeutic activity of drugs, using examples • Describe the impact that co-administered drugs can have on CYP-mediated drug metabolism, using examples • Describe the patient factors that can influence the metabolism of theophylline	