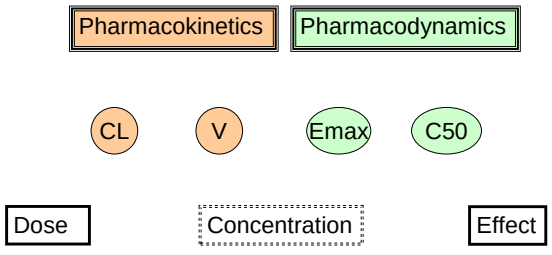
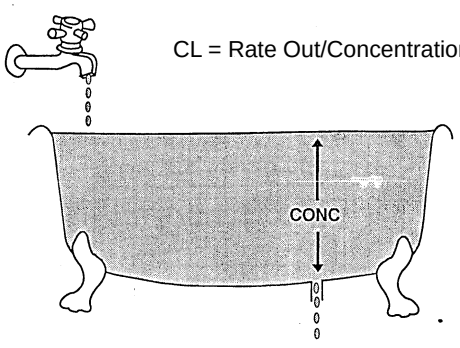
Slide 1	# Clearance Nick Holford Dept Pharmacology & Clinical Pharmacology University of Auckland, New Zealand	
Slide 2	# Pharmacology φαρμακον pharmakon Medicine Poison Magic Spell 	Pharmacology is derived from a Greek word (pharmakon). The Greeks used this word to mean a medicine, a poison or a magic spell.
Slide 3	# Clinical Pharmacology  	Clinical pharmacology describes the effects of drugs in humans. One way to think about the scope of clinical pharmacology is to understand the factors linking dose to effect. Drug concentration is not as easily observable as doses and effects. It is believed to be the linking factor that explains the time course of effects after a drug dose. The science linking dose and concentration is pharmacokinetics. The two main pharmacokinetic properties of a drug are clearance (CL) and volume of distribution (V). The science linking concentration and effect is pharmacodynamics. The two main pharmacodynamic properties of a drug are the maximum effect (Emax) and the concentration producing 50% of the maximum effect (C50).

Slide 4	# Clearance 	Clearance is the most important pharmacokinetic parameter.
Slide 5	## Objectives ➢ Learn the definition of clearance ➢ Understand the physiological determinants of clearance ➢ Be able to define clearance classes ➢ Appreciate the applications of clearance concepts to clinical practice 	
Slide 6	## Clearance *Clearance describes the relationship between concentration and the rate of elimination of drug from the body* $Rate\ Out = CL \times Concentration$ 	The definition of clearance (CL) links drug concentration to the rate of elimination (rate out). Note that elimination and clearance are NOT the same thing. Because the definition of clearance is linked directly to concentration it is important to know in what fluid the concentration is obtained. Most commonly drug clearance is based on drug concentration in plasma or serum. For all practical purposes there is no difference between plasma and serum concentrations.

Slide 7	# Theophylline Target Concentration Clin. Pharmacokinet. 25 (6): 495-505, 1993 Theophylline Target Concentration in Severe Airways Obstruction – 10 or 20 mg/L? A Randomised Concentration-Controlled Trial *Nicholas Holford*[1], *Peter Black*[1], *Ron Couch*[2], *Julia Kennedy*[3] and *Robin Briant*[1] 1 Department of Pharmacology and Clinical Pharmacology, School of Medicine, University of Auckland, Auckland, New Zealand 2 Department of Clinical Chemistry, Auckland Hospital, Auckland, New Zealand 3 Department of Pharmacy, School of Medicine, University of Otago, Dunedin, New Zealand ➢ How can a target concentration of 10 mg/L be maintained? 	A study of the effects of theophylline in patients with severe airways obstruction was carried out at Auckland Hospital. It showed that the target concentration is 10 mg/L. Higher concentrations had little extra benefit but substantially more toxicity e.g. nausea and vomiting. If the target concentration is known what dose rate is needed to maintain the concentration at the target?
Slide 8	# Maintenance Dose Rate ➢ At Steady State: $$Rate\ Out = Rate\ In$$ ➢ Therefore $$Rate\ Out = CL \cdot Concentration$$ $$mg/h = L/h \cdot mg/L$$ $$30\ mg/h = 3\ L/h \cdot 10\ mg/L$$ 	Maintenance dose rate can be predicted if the target concentration and the drug clearance are known. Steady state drug concentrations are maintained when the rate of drug administration (rate in) is equal to the rate of elimination (rate out). Using the definition of clearance we can predict the steady state rate in. Note the units of clearance are typically L/h and concentration is mg/L. Maintenance dose rates are then readily predicted with units of mg/h.
Slide 9	# Bathtub Model  	The bathtub provides a physical model to explain how clearance determines drug elimination. This bathtub has fixed rate of water flowing in from the tap (rate in = 4 drops/unit time). Water is lost from the bathtub at the same rate (rate out = 4 drops/unit time) which keeps the bath water level constant (steady state). Clearance is determined by the size of the hole in the bathtub.

Slide 10	**Physiological Basis** ➢ Liver Blood Flow » 90 L/h Upper limit for liver clearance ➢ Kidney Blood Flow » 70 L/h Upper limit for kidney clearance » Glomerular Filtration – 6 L/h All drugs » Tubular Secretion – Variable 	A key factor determining the size of clearance is the blood flow to an organ. The organ clearance cannot be any bigger than the blood flow rate. Note that clearance and blood flow are in the same units of volume/time (usually expressed as L/h) so they can be directly compared. The liver is the largest single organ responsible for drug clearance. It has a typical blood flow of 90 L/h/70 kg. The main clearance mechanism by the liver is enzyme metabolism but some drugs are also excreted unchanged in the bile. Biliary excretion does not necessarily mean elimination because drug excreted in the bile can be re-absorbed in the small intestine. The kidneys together have a combined blood flow of 70 L/h/70kg but few drugs have renal clearance approaching renal blood flow. All drugs (except for some large protein molecules) are filtered through the glomerulus but most are reabsorbed either passively or by active uptake mechanisms. Polar molecules are less likely to be re-absorbed and are excreted in the urine. The upper limit on renal clearance by glomerular filtration is the glomerular filtration rate (6 L/h/70kg). Some molecules e.g. weak acids like penicillin, are actively secreted by the tubules and can have clearances approaching renal blood flow.
Slide 11	**Physiological Basis** ➢ Very Rapid » Glyceryl trinitrate 150 L/h – plasma, liver, etc ➢ Rapid » Morphine 60 L/h – liver 	Glyceryl trinitrate is used to treat angina. It is a very unstable molecule (it is an explosive when formulated differently). It breaks down in many tissues of the body and its clearance is not limited by blood flow to a single organ. Morphine is metabolized extensively in the liver and its blood clearance (60 L/h) approaches liver blood flow. For this reason one can predict it will be extensively extracted from the blood as it passes through the liver.

Slide 12	**Physiological Basis** ➢ Medium » Gentamicin 6 L/h – Kidney » Digoxin 9 L/h – Kidney and Liver 	Gentamicin is elminated mainly by glomerular filtration so its clearance is about 6 L/h. Digoxin is cleared both by glomerular filtration but also by metabolism in the liver.
Slide 13	**Physiological Basis** ➢ Slow » Theophylline 3 L/h – Liver ➢ Very Slow » Warfarin 3 L/day – Liver 	Theophylline is mainly metabolized by the liver but its clearance is low in relation to liver blood flow. Only a small fraction is extracted as blood passes through the liver. Renal elimination of theophylline is negligible. Warfarin has very slow clearance by liver metabolism.
Slide 14	**Clearance Classification** ➢ Constant ➢ Concentration Dependent ➢ Flow Dependent 	Clearance processes can be classified depending on whether clearance is constant (i.e. apparently independent of concentration and organ blood flow), if it changes with concentration (and therefore with dose), or changes with organ blood flow. In this context clearance is considered constant within an individual without regard to unpredictable within subject variability. Concentration independent clearance is described by a first-order elimination process while concentration dependent clearance is a mixed order elimination process. Concentration independent, concentration dependent and flow dependent clearance are not exclusive properties. A drug can be eliminated by a combination of these processes. Note that although first-order clearance is constant the rate of elimination still varies with concentration.

Slide 15	**Classification** ➢ Constant » Synonyms: First Order, Linear » Examples: – Glomerular filtration – Most metabolism 	When clearance is constant (apparently independent of concentration or organ blood flow) then synonyms for the elimination process are first-order and linear. Glomerular filtration is always a first-order process. Most drug metabolism can be approximated by a first-order process because concentrations are small in relation to the Km.
Slide 16	**Classification** ➢ Concentration Dependent » Synonyms: Mixed order, non-linear, Michaelis-Menten » Examples: – Tubular secretion ▯ Penicillin – Metabolism ▯ Phenytoin 	When clearance depends on drug concentration the elimination process is called mixed-order. Synonyms are non-linear and Michaelis-Menten elimination. Renal tubular secretion of penicillin is an active process that is saturable and thus it is mixed-order. Metabolism of phenytoin (a commonly used anticonvulsant) is saturable at doses close to those used clinically.
Slide 17	**Concentration Dependent Clearance**  $Rout = \left[\frac{V\max}{Km + C}\right] \cdot C$ Mixed Order  $Rout = \left[\frac{V\max}{Km + C}\right] \cdot C$ $Rout = CL \cdot C$ First Order $Rout = \left[\frac{V\max}{Km + C}\right] \cdot C$ $Rout = V\max$ Zero Order 	Rout = Rate out The order of a chemical reaction can be defined in terms of the number of reactive species determining the rate of the reaction (https://en.wikipedia.org/wiki/Order_of_reaction). Enzymatic reactions are typically saturable and can be described in terms of the maximum rate of elimination (Vmax) and the concentration producing 50% of Vmax (Km). Most enzymatic drug metabolism (i.e. elimination) is driven primarily by the drug concentration. If concentration is small in relation to Km then the elimination rate will appear to be first-order i.e. linearly dependent only on concentration. If concentrations are large in relation to Km then the elimination rate will appear to be independent of concentration. This is called a zero-order reaction. Concentrations that are neither small nor large in relation to Km will give rise to a mixed-order reaction. The mixed-order reaction should be considered as

		the general case for all drugs eliminated by metabolism. The first-order approximation is very common. True zero-order elimination does not occur in reality but may be approximated at very high concentrations.
Slide 18	**Classification** ➢ Flow Dependent » Synonym: Organ specific clearance » Example: – Morphine ©NHG Holford, 2021 all rights reserved.	When clearance is flow dependent it is usually associated with elimination by the liver. Morphine is an example of a drug with clearance dependent on blood flow. If morphine is given to patients with heart failure the liver blood flow is reduced because of heart failure and so clearance can be quite low. This means the maintenance dose should be reduced.
Slide 19	**Applications** ➢ Maintenance Dose $\text{Maintenance Dose Rate} = CL \cdot \text{Target Conc}$ ➢ Half-Life $T_{\frac{1}{2}} = \frac{0.7 \bullet V}{CL}$ ©NHG Holford, 2021 all rights reserved.	The main clinical application of understanding about clearance is for prediction of the maintenance dose rate. A second useful application is the ability to calculate the half-life. This requires the volume of distribution (V) to be known as well as clearance.

Slide 20	# Applications ➢ Additional elimination processes » Haemodialysis » Haemoperfusion » Gut adsorption (charcoal) 	The benefits of treatments intended to enhance elimination after poisoning can be evaluated by comparing the clearance by the treatment to the expected drug clearance without treatment. Haemodialysis is the same procedure used for patients with renal failure. Haemodialysis clearance is relatively low. For example, haemodialysis clearance of theophylline is 4 L/h. While this is low compared to clearance of other drugs it is similar to the metabolic clearance of theophylline and thus can substantially increase theophylline elimination. Haemoperfusion involves passing blood through a cartridge designed to adsorb the drug. Haemoperfusion clearance can be double that of haemodialysis (e.g. theophylline haemoperfuson clearance is 9 L/h) but there is wide drug to drug variability (Cutler, R.E., Forland, S.C., Hammond, P.G.S. & Evans, J.R. Extracorporeal Removal of Drugs and Poisons by Hemodialysis and Hemoperfusion. *Annu Rev Pharmacol Toxicol* **27**, 169-91 (1987)). Adsorption of drug in the gut by activated charcoal can enhance elimination by preventing primary absorption and re-absorption from drug passing from the body passively back into gut fluids. Activated charcoal can double theophylline clearance from 3 L/h to 6 L/h.