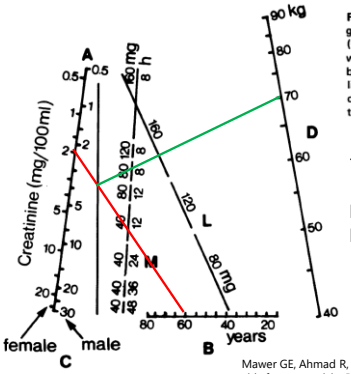
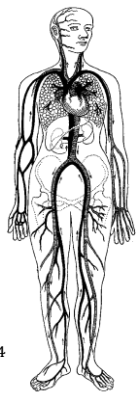
Slide 1	# Nomogram to NextDose Body Size, Maturation and Organ Function Nick Holford Dept Pharmacology & Clinical Pharmacology University of Auckland	Presented on the occasion of being awarded the American College of Clinical Pharmacology Distinguished Investigator award 17 Sep 2017, San Diego, CA, USA.
Slide 2	# Gentamicin Nomogram  **Fig. 1** Nomogram for gentamicin dosage. The nomogram provides a loading dose (L), a maintenance dose (M) and a suitable interval between doses for a patient whose serum creatinine concentration (A), age (B) and body weight (D) are known. To use, join A to B with a line which cuts C, then join C to D with a line which cuts L and M. A more detailed description is given in the text. 70 kg 60 y male Scr 2 mg/dL Loading Dose: 160 mg Maintenance Dose: 80 mg q8h Mawer GE, Ahmad R, Dobbs SM, McGough JG, Lucas SB, Tooth JA. Prescribing aids for gentamicin. Br J Clin Pharmacol. 1974;1(1):45-50. 	My first job as a medical doctor was a House Surgeon at Macclesfield Hospital in 1972. I only did minor surgery but I won acclaim from my surgical colleagues for predicting doses of gentamicin using George Mawer's nomogram. The nomogram uses weight, age, sex and serum creatinine for loading and maintenance doses. Dosing was always 8 hourly. I carried paper copies of the nomogram with my in my pocket and could quickly recommend a dose in patients needing gentamicin for treating surgical infections. There were no measurements of gentamicin available at that time so there was no question of further individualization.
Slide 3	# **Body Size** is the most important quantitative determinant of drug dose - The **human body weight range** varies from about 500 g to over 250 kg due to both biological variability and changes over the lifespan. - This more than **500 fold** range in size is directly translatable through volume of distribution into drug **loading dose** differences - Because of allometrically predictable relationships beween weight and clearance the corresponding range of **maintenance dose rates** is only about **100 fold** 	Shortly before I took up my first medical job in 1972 I was examined orally for and won a prize for medicine. One of the exam questions was how to individualize the use of azathioprine (a question asked by a neurologist). I figured out the answer was to use weight and prescribe a mg/kg dose. At the time that was considered highly sophisticated. Today we can recognize that weight is the most important single covariate for dose individualisation in humans. Weight explains at least a 100 fold difference in dose in order to maintain a target concentration.

Slide 4

Theoretical Foundation for Allometric Scaling



$$CL_{CHILD} = CL_{ADULT} \times \left(\frac{WT_{CHILD}}{WT_{ADULT}}\right)^{3/4}$$

West GB, Brown JH, Enquist BJ. The fourth dimension of life: fractal geometry and allometric scaling of organisms. Science. 1999;284(5420):1677-9.

The fundamental assumption of West's allometric theory is that all cells are similar in size and have similar energy requirements. The structure of the energy delivery system e.g. blood vessels in humans, requires a certain mass e.g. bones in humans, to support the delivery system as well as the target cells. The mass overhead from these delivery and support systems increases total body mass without a linear increase in function. The allometric exponent value of ¾ describes this non-linear relationship for clearance. This concept is true for both animals (e.g humans or elephants) and plants (e.g. sequoia or kauri).

In contrast to functional processes such as clearance, allometric theory predicts a linear relationship between mass and structural properties such as volume of distribution. The allometric exponent for volume of distribution is 1.

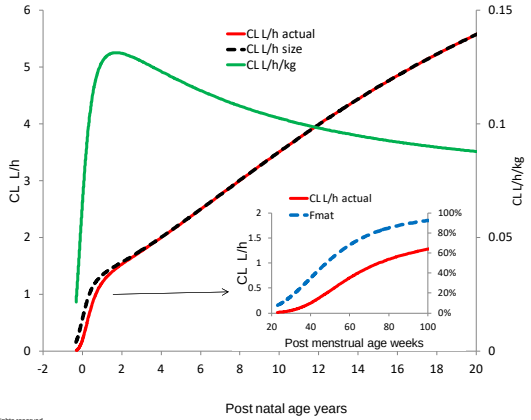
Photo shows Nick Holford (41 y 80 kg) and Sam Holford (1 y 8 kg) on Fox Glacier, NZ 1987

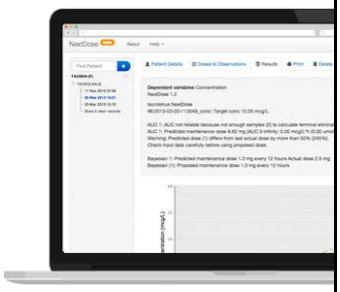
Slide 5

Renal Function

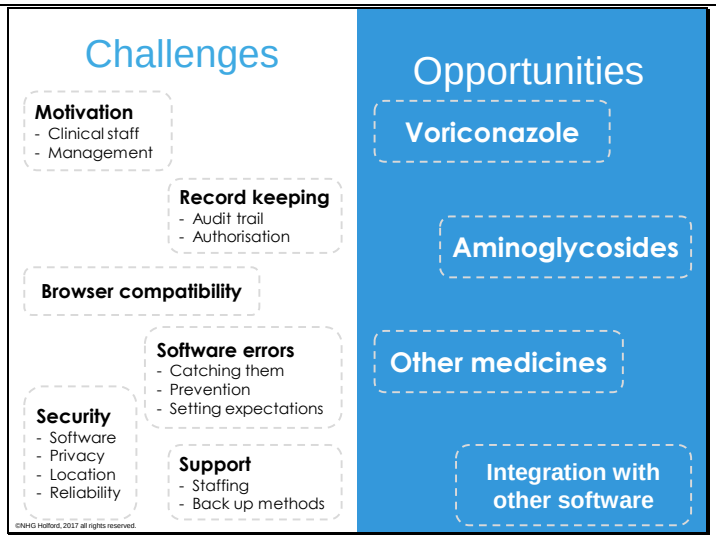
- **Differences in renal function** can explain about a **10 fold difference in total drug clearance**.
- Glomerular Filtration Rate
  - » 7 L/h in healthy young adult
  - » 0.5 L/h in terminal renal failure
- There is always some non-renal clearance e.g. via the gut which adds 0.5 L/h to renal clearance even in renal failure

Renal function based on GFR are important but still less than weight after accounting for body size.

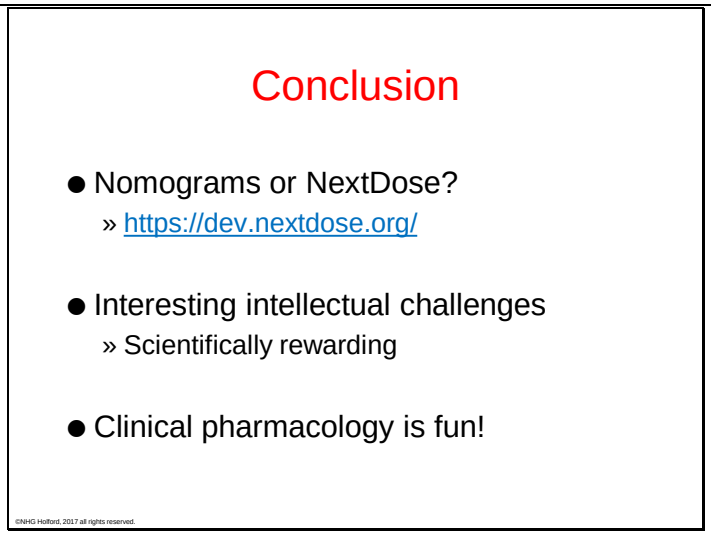
Slide 6	**Hepatic Function** ● **Difficult to predict hepatic drug clearance without administering the drug** ● "Liver Function Tests" » measure liver damage which is not the same as function ● Clinical Staging Systems » Childs Pugh system/MELD/HPSE » Loosely correlated with hepatic drug clearance 	Population predictions of hepatic function are possible but individual predictions do not have any reliable biomarkers like serum creatinine for renal function. MELD=Model for Evaluation of Liver Disease HPSE=Hepatic Portal Systemic Elements
Slide 7	**Maturation and Ageing** • **Maturation Of Drug Clearance** • Typical maturation is about 30% of adult values at full term delivery • Very premature neonates are around 10% of adult values • In neonates and infants age accounts for a 10 fold increase in glomerular filtration rate from 24 weeks post-menstrual age up to 1 year of post-natal age (Rhodin et al. 2009). • **Ageing and Drug Clearance** • Age in older adults has a minor (~ 25% lower) influence on drug clearance once weight and other factors such as renal function are accounted for. 	There is a very important biological difference between age in young humans and old humans. Young humans (babies, infants) are immature. They have size appropriate organs but have not yet developed functional capacity. Old humans lose renal function as a consequence of nephron loss related to environmental hazards (not age) but do not lose hepatic function because the liver regenerates its cells and enzymes irrespective of age. Rhodin, M. M., B. J. Anderson, A. M. Peters, M. G. Coulthard, B. Wilkins, M. Cole, E. Chatelut, A. Grubb, G. J. Veal, M. J. Keir and N. H. Holford (2009). "Human renal function maturation: a quantitative description using weight and postmenstrual age." Pediatr Nephrol **24(1): 67-76.**
Slide 8	**Weight and Age Explain Higher mg/kg Doses in Young Children**  	Clearance increases with weight and age (red line). Allometric size predicts increasing clearance per kg with lower weights (green line). Below 2 years of age immaturity of drug clearance has a major effect on clearance (see inset) so clearance per kg decreases. This leads to a peak in clearance when expressed per kg around 2 years of age. Maintenance doses are commonly expressed per kg in clinical practice and are also higher around 2 years of age than in babies and adults. The green line (clearance/kg) is consistent with long standing empirical knowledge of drug dosing in children. It is explained by the combination of two biological processes – size and maturation.

Slide 9	**NextDose** ○ Bayesian forecaster ○ Published models - busulfan - methotrexate - tacrolimus - warfarin - linezolid ○ Simple on the outside ○ Browser-based web app ○ Cloud hosted  	NextDose was developed in collaboration with my son, Sam Holford (see Slide 4). He created the web interface to the modelling backend that I worked on. Sam is now a practicing medical doctor. We continue to work on developing NextDose.
Slide 10	**Technology** ○ Software abstraction layers ○ NONMEM core - NMTRAN input - Bayesian methodology ○ awk pre & post processor - Dose proposal - Concentration predictions ○ PHP + MySQL middleware - User + clinical record keeping - Translation to/from Awk ○ HTML5 + JavaScript UI  	
Slide 11	**A collaborative effort** **Clinicians** ○ age ○ weight ○ disease **Pharmacists** ○ formulation ○ dose ○ time **Phlebotomists & nurses** ○ blood sample time **Laboratory** ○ concentration determination Common interface for use at different times and locations for all involved 	

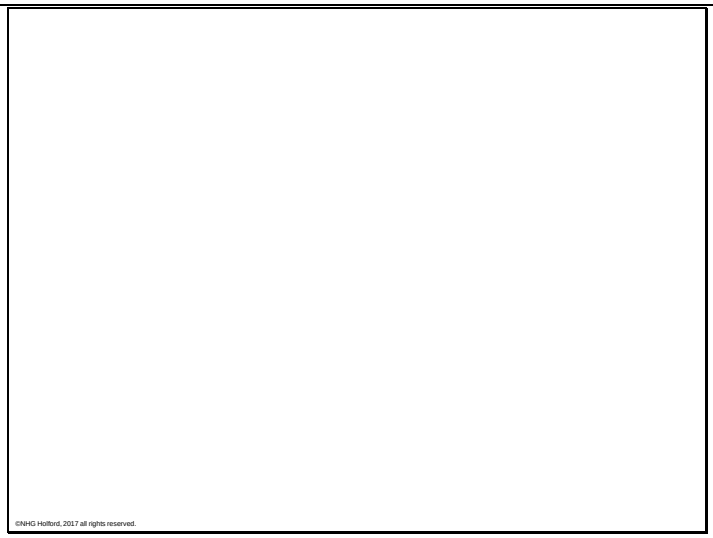
Slide 12



Slide 13



Slide 14



Slide 15

Rules of PNA and PMA

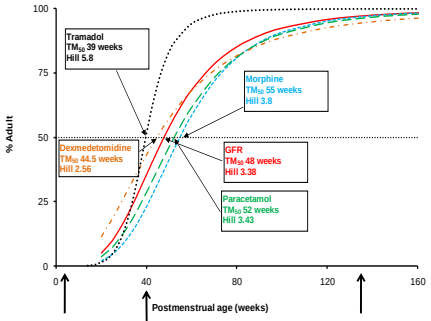
Fraction of adult maintenance dose

Typical Weight Kg	PMA or PNA	Fraction Adult Dose	Rule of PMA+PNA Error	'true' % Adult Dose
1	25 weeks	1/300	10%	0.3
1	30 weeks	1/120	1%	0.8
3	Full Term	1/30	1%	3.3
6	3 mo	1/10	8%	9.3
7	6 mo	1/6	24%	13.4
9	1 year	1/5	3%	19.5
12	2 years	1/4	-4%	26.1
19	5 years	1/3	-11%	37.4
34	10 years	1/2	-14%	58.5
50	15 years	3/4	-3%	77.4
70	Adult	1		100.0

Weight is combined with post-natal age (PNA) and post-menstrual age (PMA) to predict the typical dose as a % of the adult dose.
The coloured areas of the table show the fraction of adult maintenance dose that would be expected for infants and children. The fractions are based on the theoretical size and maturation model for typical drug clearance with some approximation to make the numbers easier to remember. The 'rule of PMA+PNA' has an acceptable error for clinical dose prediction.
Although maturation is best described by a non-linear relationship it is quite well approximated by a linear function of PMA.

Slide 16

Clearance Maturation



Conception

Full Term

2 years old

Maturation is complete by 2 years of age –

– then weight is the sole predictive factor for drug clearance

Post-menstrual age is the recommended way to describe the biological age in weeks after conception. It is based on the mother's recall of the date of the last menstrual period. It is therefore typically biased by overestimating the age since conception by 2 weeks.