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## Environmental Variability

### Body Size, Body Composition, Maturation and Organ Function

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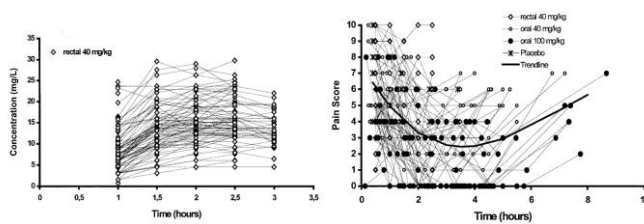
## Objectives

- Understand the major sources of variability affecting the response to medicines
- Appreciate the relative contributions of body size, body composition, maturation and organ function to variability
- Learn the principles of dose individualization based on predictable sources of variability

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## Paracetamol Variability: Concentration and Response

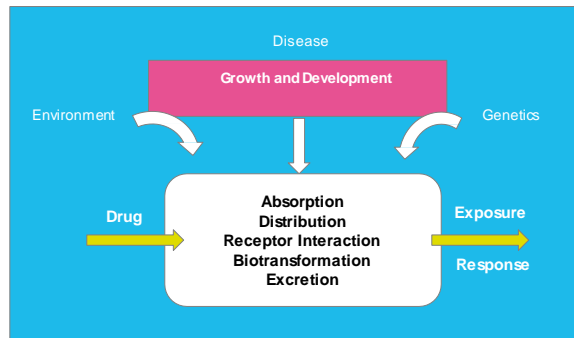


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Anderson BJ, EJCP 2001

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## Drug Response



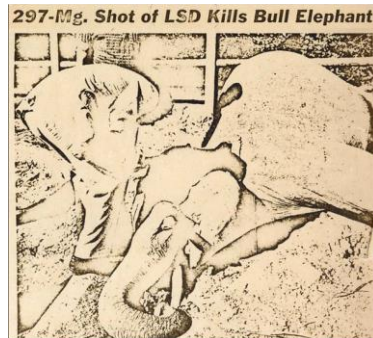
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## An elephant and LSD

In 1962 a group of “researchers” (led by a psychiatrist called Jolly West) injected a poor elephant (named Tusko) with 297 mg of LSD. They wanted to know if LSD induced musth in elephants. After being darted with an LSD-containing syringe, the elephant

“...trumpeted, collapsed, fell heavily into its right side, defecated, and died.”



How did the “researchers” determine the dose?

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## 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 between weight and clearance the corresponding range of **maintenance dose rates** is only about **100 fold**

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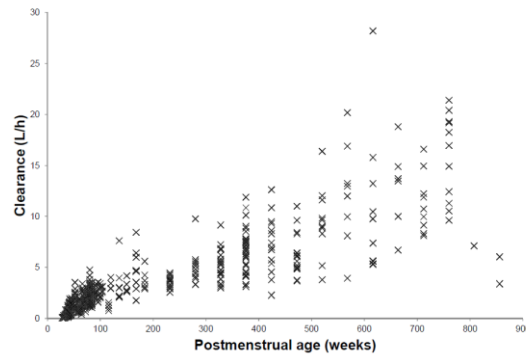
## PK Determining Dose Dose determines concentration

- **Volume of distribution**
  - Initial dose
- **Clearance**
  - Maintenance dose

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## Paracetamol clearance variability

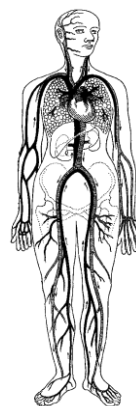


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Anderson BJ, EJCP 2001

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## Theoretical Foundation for Allometric Scaling (Fractal Geometry)



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

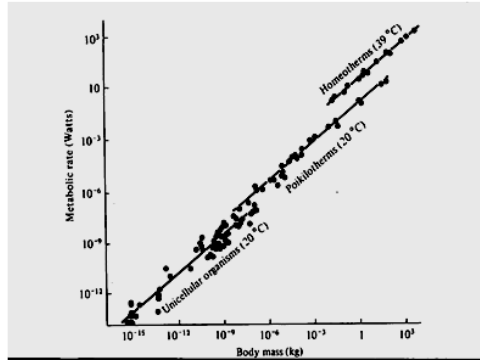
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West GB, Brown JH, Enquist BJ. The fourth dimension of life: fractal geometry and allometric scaling of organisms. *Science*. 1999;284(5420):1677-9.

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  $3/4$  describes this non-linear relationship for clearance. 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.

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## Allometric Size Matches Observations 18 Orders of Magnitude

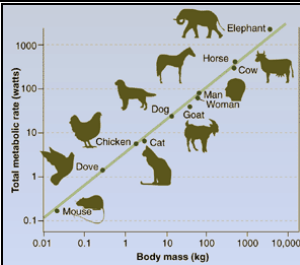


**Kleiber's law**, (named after Max Kleiber) - For the vast majority of animals, an animal's metabolic rate scales to the  $\frac{3}{4}$  power of the animal's mass.

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Peters R. The ecological implications of body size. Cambridge: Cambridge University Press; 1983.

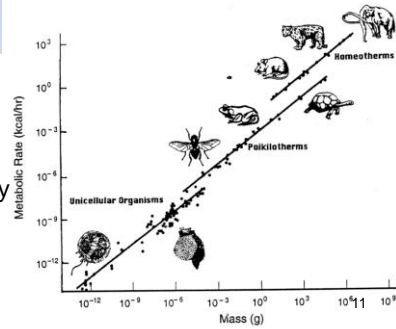
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The relationship between metabolic rate and body mass is remarkably robust and works across a large number of animals.

Why does it matter...

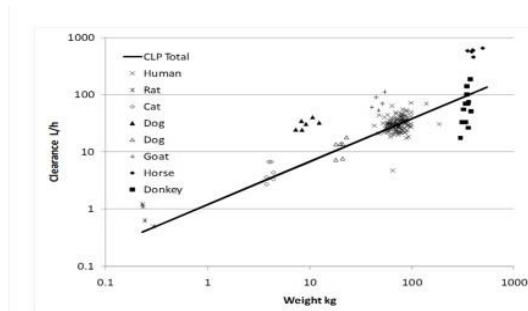
It is important because a great number of biologically important features of an organism depend on metabolic rate..



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## Tramadol Clearance



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Holford S. JPharmacol Clin Toxicol 2014

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## What happened to Tusko?

207-715: Shot of LED Kills Bull Elephant



### Human

0.02mg/1kg = 1.4mg/70kg

### Elephant

= 70mg/3500kg

### Cat

0.1mg/1kg = 0.5mg/5kg

### Elephant

= 350mg/3500kg

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## Drug Dose

Animal	Mass (kg)	Metabolic Rate ml O <sub>2</sub> /g/h	Dose Based on Metabolic Rate (mg)
Cat	20	0.3	2 (0.1mg/kg)
Human	70	0.2	4.7 (0.06mg/kg)
Elephant	3500	0.1	117 (0.033mg/kg)

### 250% Overdose

Body mass is the main determinant of the magnitude of most physiological processes (such as metabolic rate). So “Scaling-up” a physiological process (and hence a dose) is not completely uninformed. **However,**

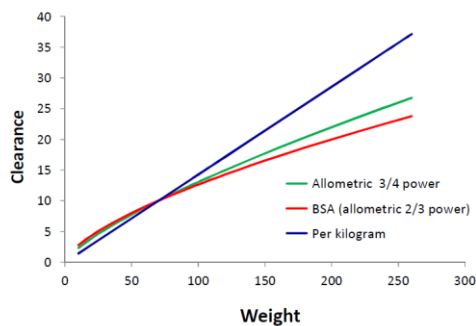
**Log Metabolic Rate vs Log Body Mass: The slope of the line is not 1**

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## Clearance changes with weight

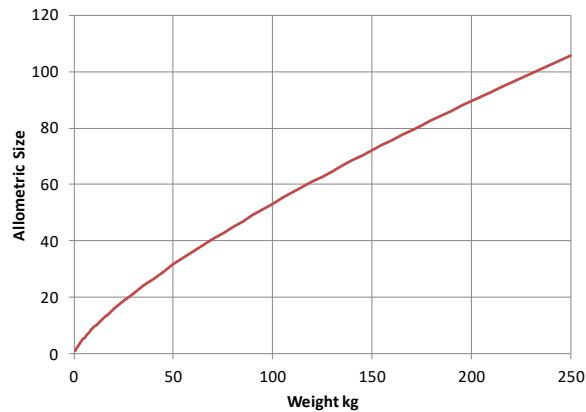


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Anderson BJ. Arch Dis Child 2013; 98: 737.

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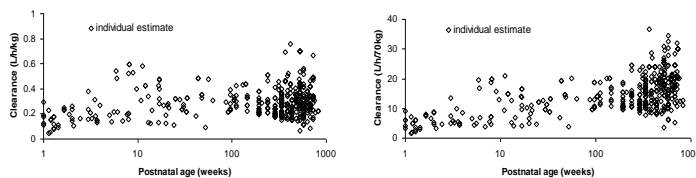
## Allometric Size for Clearance



The relationship between weight and clearance is non-linear. It is predictable from theory based allometry. Allometric size is scaled in this figure relative to a value of 1 at a weight of 0.5 kg. With weight varying 500 fold from 0.5 kg to 250 kg the equivalent allometric size varies by a factor of just over 100.

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## Paracetamol - Age vs Clearance



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## Which Age?

- Post-natal age (PNA)
  - » Does not account for *in utero* maturation
- Post-menstrual age (PMA)
  - On average 2 weeks longer than biological age
- Post-conception age (PCA)
  - The biological age but not widely recorded

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The age of a baby may be described using several kinds of “age”.

Post-natal age (PNA). This is the age (e.g. days) since birth. It does not account for *in utero* maturation of body structure and function.

Post-menstrual age (PMA). This is the age (e.g. weeks) since the mother’s last menstrual period. On average it is 2 weeks longer than biological age

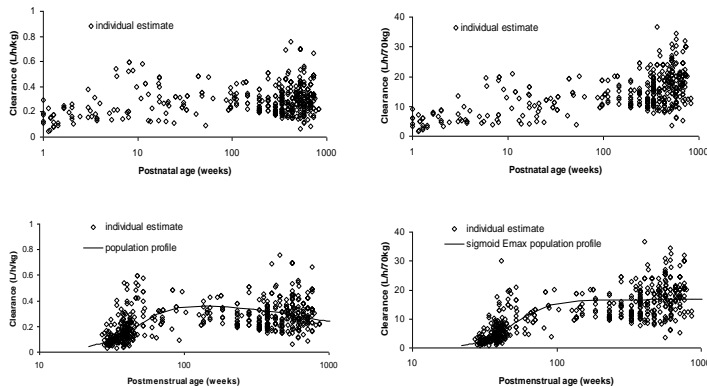
Post-conception age (PCA). This is the age (e.g. weeks) since conception. This is the best description of biological age but it is not widely recorded because the date of conception is often difficult to identify.

Gestational age (GA). Defined by the PMA at birth. GA does not change with time.

Post menstrual age is the recommended way to describe biological age. This recommendation is pragmatic rather than theoretically correct.

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## Paracetamol - Age vs Clearance

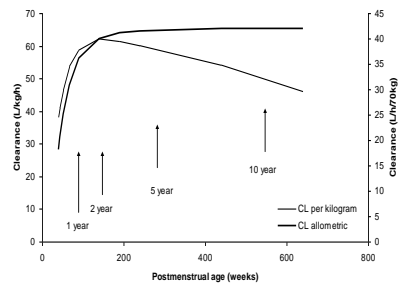


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Anderson BJ. Drug Metab. Pharmacokint. 2009; 24(1): 25-36.

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## Dexmedetomidine Maturation



Potts A. *Pediatr Anesth* 2009

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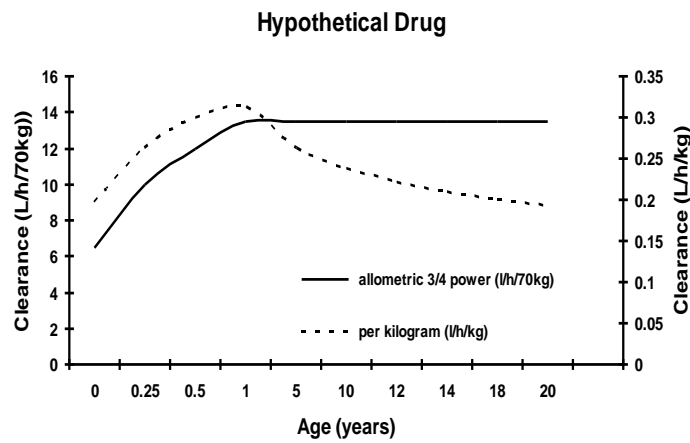
## Maturation and Ageing

- **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.

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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.

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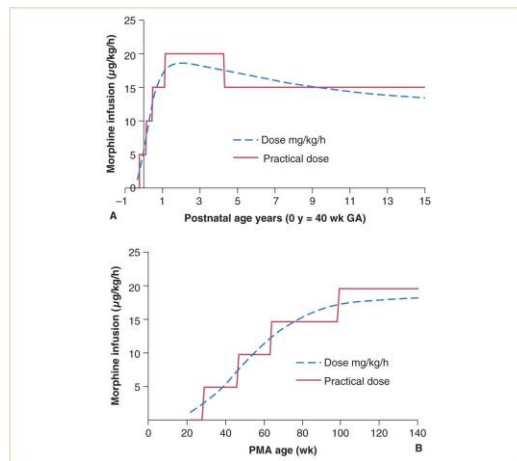


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Anderson BJ. *Pediatr Anest* 2002;12: 205

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## Morphine Dosing



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Anderson BJ, Holford NH. *Arch Dis Child*. 2013;98:737-744

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## Morphine infusion

- target concentration 10 mg/L

➤ Birth	5	mcg/kg/h
➤ 1 Month	8.5	mcg/kg/h
➤ 3 Months	13.5	mcg/kg/h
➤ 1 Year	18	mcg/kg/h
➤ 2 Year	16	mcg/kg/h

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## 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

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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.

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## Body Composition

- Simplest view of body composition is to distinguish between fat free mass and fat mass
- Fat mass is typically around 22% of total body weight (men) and 28% (women)
- Fat free mass is predictable from total body weight, height and sex (Janmahasatian 2005)
- Drug clearance and volume of distribution is 'driven' mainly by fat free mass but also by fat mass. The fraction of fat mass predicting drug elimination and distribution varies from drug to drug.

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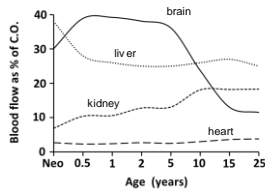
[http://en.wikipedia.org/wiki/Body\\_fat\\_percentage](http://en.wikipedia.org/wiki/Body_fat_percentage)

The fraction of fat mass predicting drug elimination and distribution varies from drug to drug e.g. 0 for warfarin clearance and volume (Xue et al 2017), 0.509 for busulfan clearance and 0.203 for busulfan volume (McCune et al. 2014) and 1 for propofol clearance and volume (Cortinez et al. 2010). These fractions are multiplied by fat mass to predict the equivalent fat free mass determining either clearance or volume. The resulting sum of fat free mass and fraction of fat mass is called normal fat mass. Normal fat mass is used in allometric scaling to combine body mass and body composition. Janmahasatian S, Duffull SB, Chagnac A, Kirkpatrick CM, Green B. Lean body mass normalizes the effect of obesity on renal function. Br J Clin Pharmacol. 2008;65(6):964-5. Xue L, Holford N, Ding XL, Shen ZY, Huang CR, Zhang H, et al. Theory-based pharmacokinetics and pharmacodynamics of S- and R-warfarin and effects on international normalized ratio: influence of body size, composition and genotype in cardiac surgery patients. Br J Clin Pharmacol. 2017;83(4):823-35. McCune JS, Bemer MJ, Barrett JS, Scott Baker K, Gamis AS, Holford NHG. Busulfan in Infant to Adult Hematopoietic Cell Transplant Recipients: A Population Pharmacokinetic Model for Initial and Bayesian Dose Personalization. Clin Cancer Res. 2014;20(3):754-63.

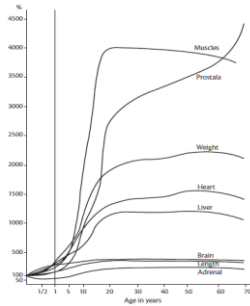
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## Growth

- organ size
- organ blood flow



Blaissomette B. Pediatric anesthesia: basic principles, state of the art, future. PMPH-USA; 2011, p 356

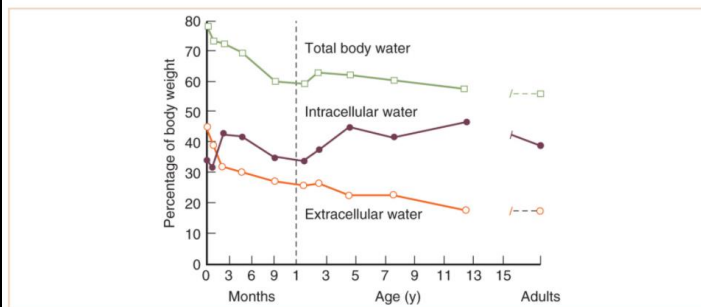


Fitz-Hansen, B. (1971). "Body composition during growth. In vivo measurements and biochemical data correlated to differential anatomical growth." *Pediatrics* 47(1): Suppl 2:264

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## Body Water



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*Pediatrics* 1961;28: 169-181

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## 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

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## Prediction of Renal Function

- **Serum Creatinine is Used to Calculate Creatinine Clearance (CLcr)**
  - » Adults:
    - Cockcroft & Gault, MDRD and eGFR
  - » Children and babies
    - Schwartz
- CLcr is approximately the same as glomerular filtration rate
- Renal function is calculated relative to normal CLcr for weight and age:

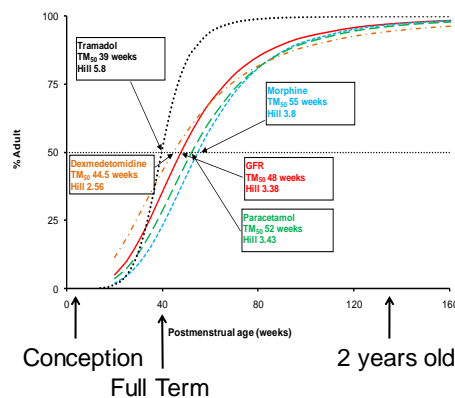
$$\text{Renal Function} = \frac{\text{Predicted CLcr}}{\text{Normal CLcr}}$$

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Cockcroft & Gault method is recommended for prediction of drug clearance. The formula is based on clearance concepts and uses weight, age and sex to predict creatinine production rate based on expected muscle mass. Schwartz methods developed for children and babies using height as a measure of body size. MDRD and eGFR methods developed for diagnosis of different categories of renal function. These are empirical formulae that do not include body size (Levey et al. 1999). Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron*. 1976;16:31-41. Schwartz GJ, Munoz A, Schneider MF, Mak RH, Kaskel F, Warady BA, et al. New Equations to Estimate GFR in Children with CKD. *J Am Soc Nephrol*. 2009:ASN.2008030287. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. *Ann Intern Med*. 1999;130(6):461-70.

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## Clearance Maturation



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.

This presentation was made by a clinical pharmacologist (Paolo Denti) with some helpful advice about using allometry and maturation concepts. <https://www.rosaandco.com/webinars/2020/what-drives-policy-change>

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Anderson BJ, Holford NH. *Paediatr Anaesth*. 2011;21:222-237

<p>Slide 32</p>	<h2 style="text-align: center;">Hepatic Function</h2> <ul style="list-style-type: none"> <li>➤ <b>Difficult to predict hepatic drug clearance without administering the drug</b></li> <li>➤ “Liver Function Tests” <ul style="list-style-type: none"> <li>» measure liver damage which is not the same as function</li> <li>» AST/ALT may be very high (1000s) in viral hepatitis with no changes in hepatic drug clearance</li> <li>» Albumin and INR changes in terminal hepatic failure are correlated with hepatic drug clearance</li> </ul> </li> <li>➤ Clinical Staging Systems <ul style="list-style-type: none"> <li>» Child-Pugh system</li> <li>» Loosely correlated with hepatic drug clearance</li> </ul> </li> </ul> <p><small>©NHG Halford, 2021 all rights reserved.</small></p>	
<p>Slide 33</p>	<h2 style="text-align: center;">Body size, renal function and post-menstrual age are the most important determinants of drug dose</h2> <ul style="list-style-type: none"> <li>➤ In comparison to these factors other covariates such as <b>genotype often pale into insignificance.</b></li> <li>➤ Quantitative pharmacology can help put the role of using covariates to predict drug dose into a <b>realistic perspective.</b></li> </ul> <p><small>©NHG Halford, 2021 all rights reserved.</small></p>	<p>Rothwell PM, Cook NR, Gaziano JM, Price JF, Belch JFF, Roncaglioni MC, et al. Effects of aspirin on risks of vascular events and cancer according to bodyweight and dose: analysis of individual patient data from randomised trials. <i>The Lancet</i>.</p> <p>Theken KN, Grosser T. Weight-adjusted aspirin for cardiovascular prevention. <i>The Lancet</i>. 2018;392(10145):361-2.</p>
<p>Slide 34</p>	<h2 style="text-align: center;">Assessment Short Answer Question Examples</h2> <ol style="list-style-type: none"> <li>1. What are the major determinants of between subject differences in clearance? Give approximate relative importance of the determinants in numerical terms.</li> <li>2. Draw a graph of the relationship between body mass and clearance and body mass and volume of distribution over the human weight range.</li> <li>3. Why are doses per kg typically larger in children when compared to adults?</li> </ol> <p><small>©NHG Halford, 2021 all rights reserved.</small></p>	