

Children are not small adults

**Adults are BIG children &
Children are OLD babies**

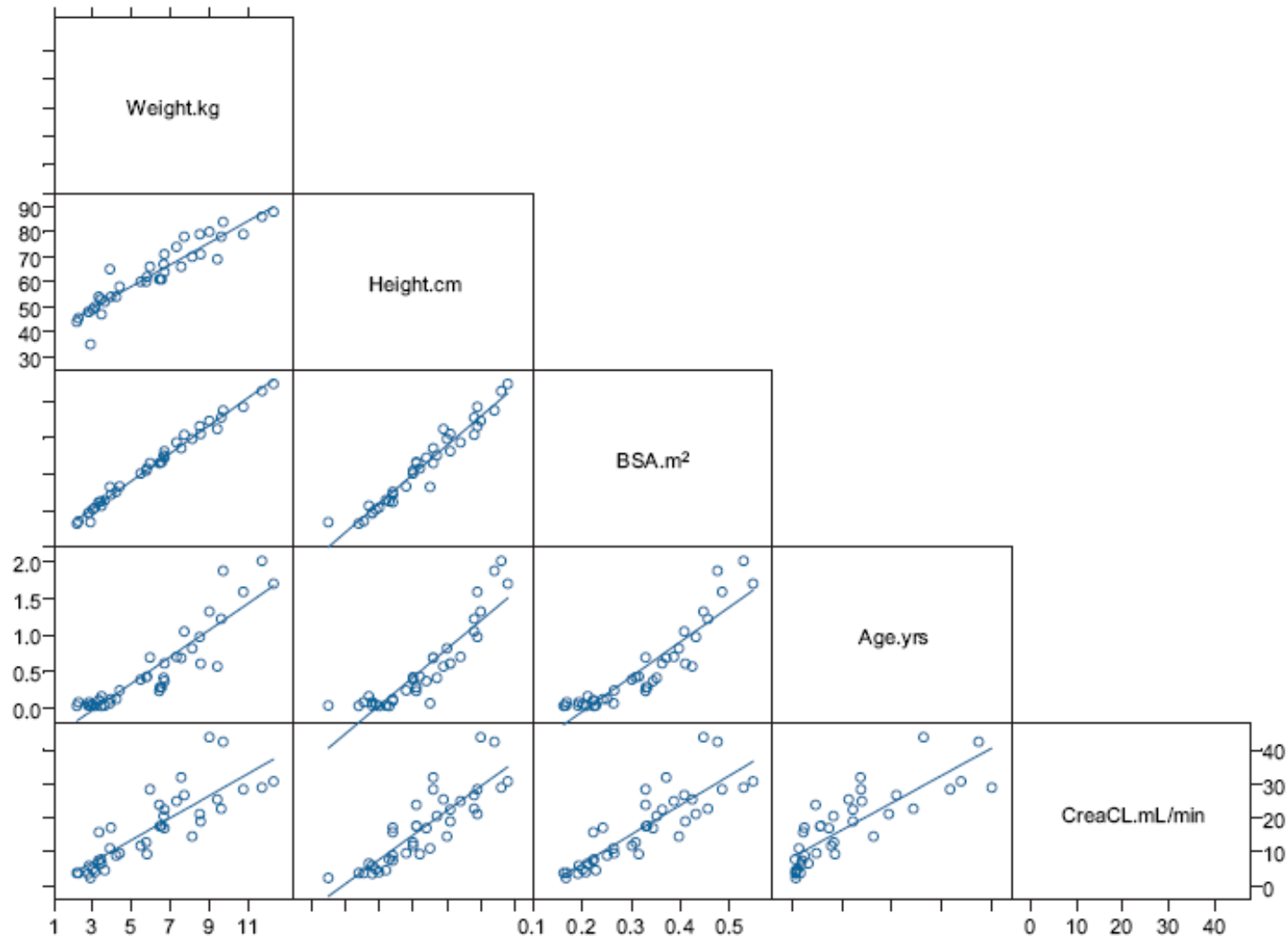
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New Zealand**

Example for colinearity in a pediatric covariate data set

(n=40; age range 12 days to 2 years)

(Meibohm B. The AAPS Journal 2005)



The Major PK Covariates in Children

- **SIZE**
- **AGE**
- **Organ Function**
- **Body Composition**
- Drug interactions
- Pharmacogenetics
- Environmental factors
- Circadian rhythms

Require a mechanistic approach

CLEARANCE: A Mechanism Based Model

$$CL_{GRP} = CL_{STD} \cdot \left(\frac{WT}{WT_{STD}} \right)^{3/4} \cdot MF \cdot OF$$

The diagram illustrates the Clearance Mechanism Based Model equation. The equation is $CL_{GRP} = CL_{STD} \cdot \left(\frac{WT}{WT_{STD}} \right)^{3/4} \cdot MF \cdot OF$. Annotations include: a red circle around the weight ratio term $\left(\frac{WT}{WT_{STD}} \right)^{3/4}$ with an arrow pointing to a black box labeled 'Size'; a red circle around 'MF' with an arrow pointing to a white box labeled 'Maturation'; and a red circle around 'OF' with an arrow pointing to a white box labeled 'Organ Function'.

CL_{GRP} = Group clearance

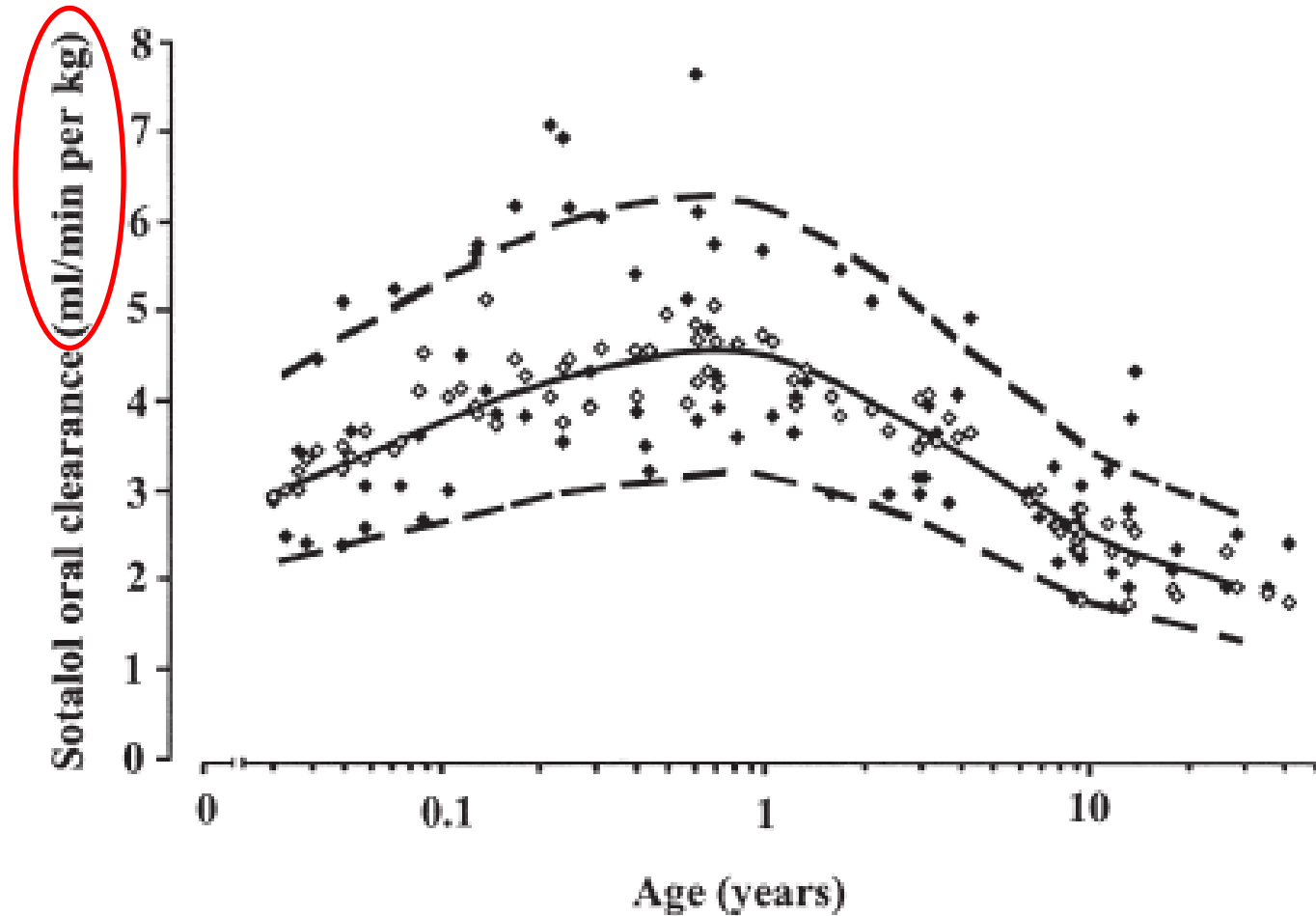
CL_{STD} = Population standard clearance

WT = Total Body Weight

WT_{STD} = Standard weight e.g. 70 kg

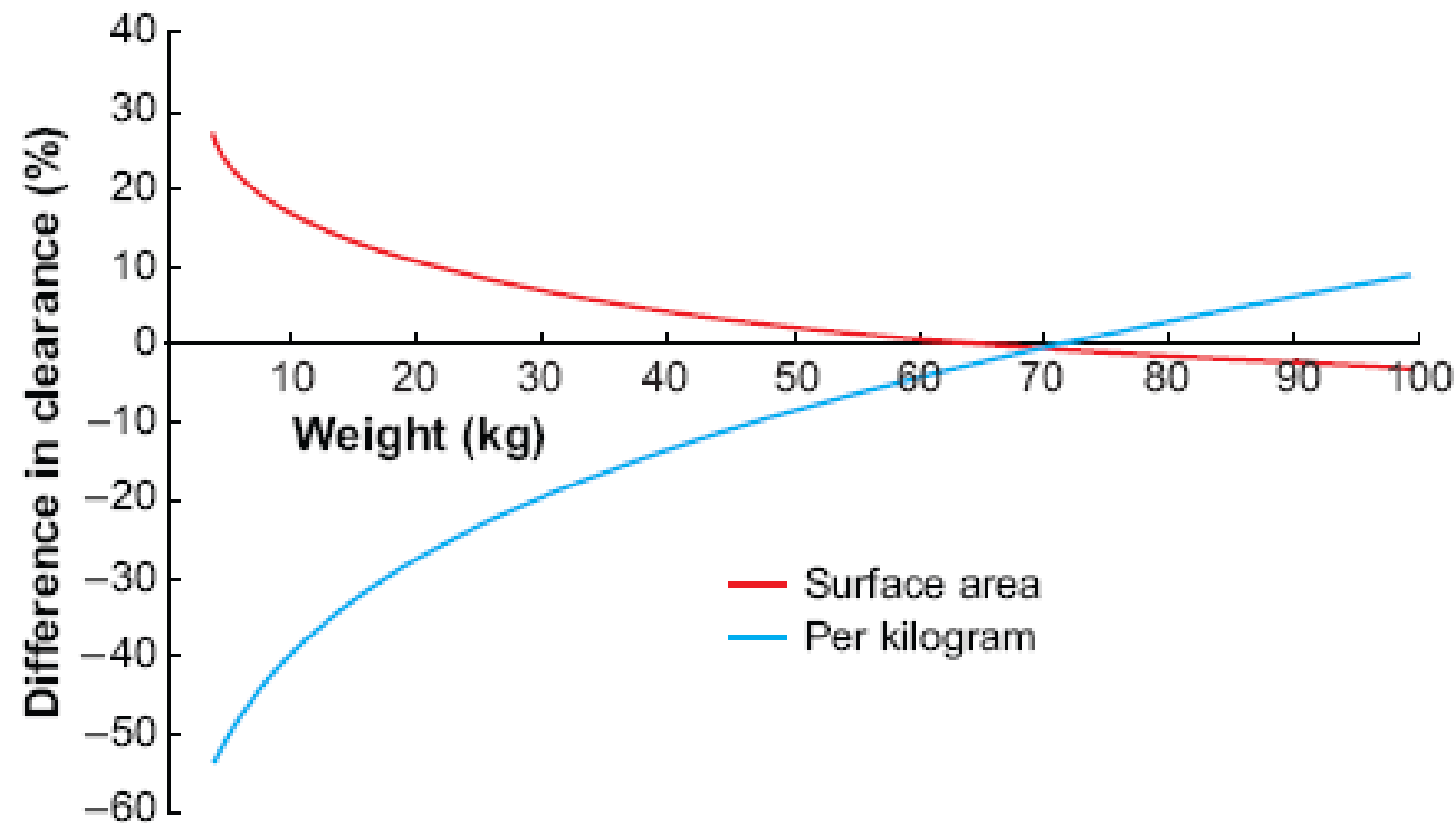
Scaling Size in Humans

Size, Age and Clearance

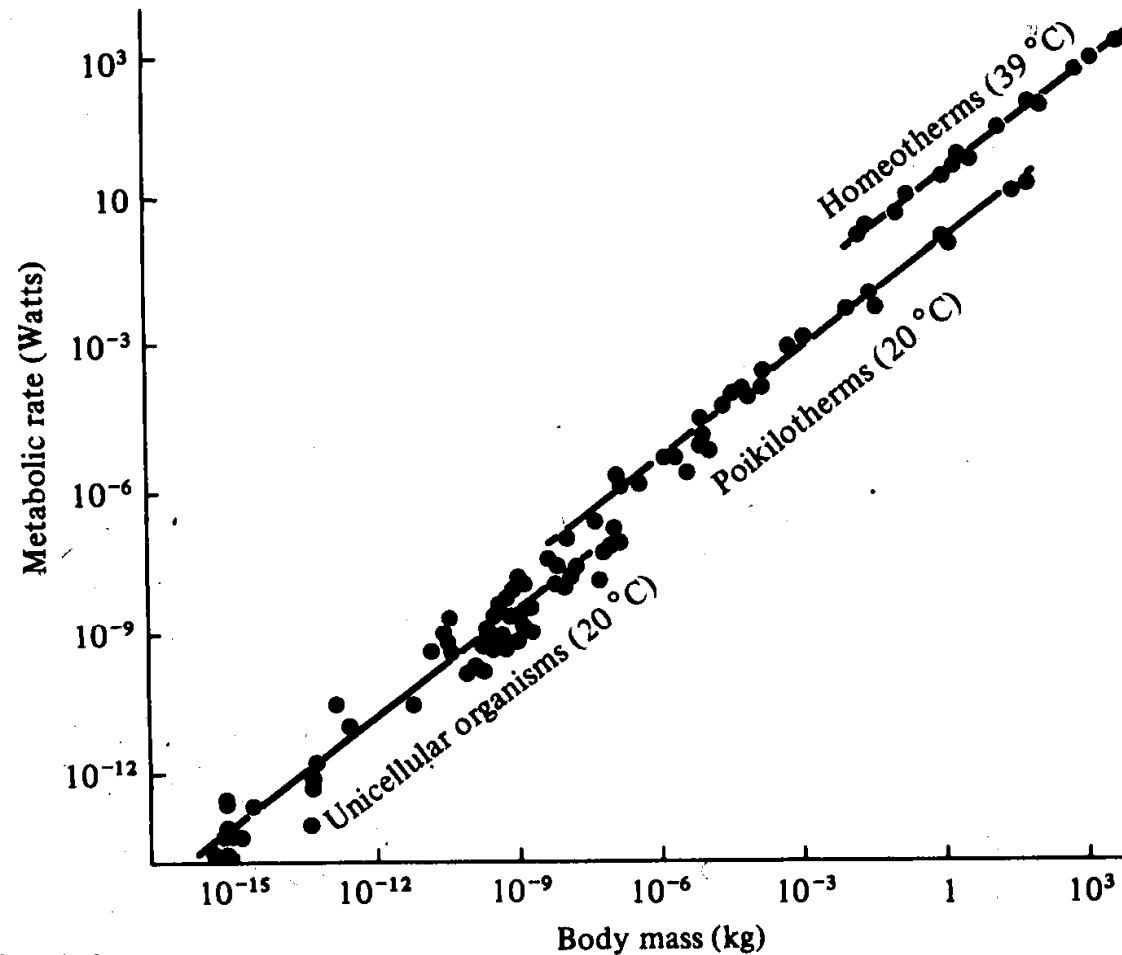


Laer S, Elshoff JP, Meibohm B, Weil J, Mir TS, Zhang W, et al. Development of a safe and effective pediatric dosing regimen for sotalol based on population pharmacokinetics and pharmacodynamics in children with supraventricular tachycardia. *J Am Coll Cardiol.* 2005;46(7):1322-30.

Percent differences in clearance determined by the surface area and per kilogram models when compared with the allometric $3/4$ power model.

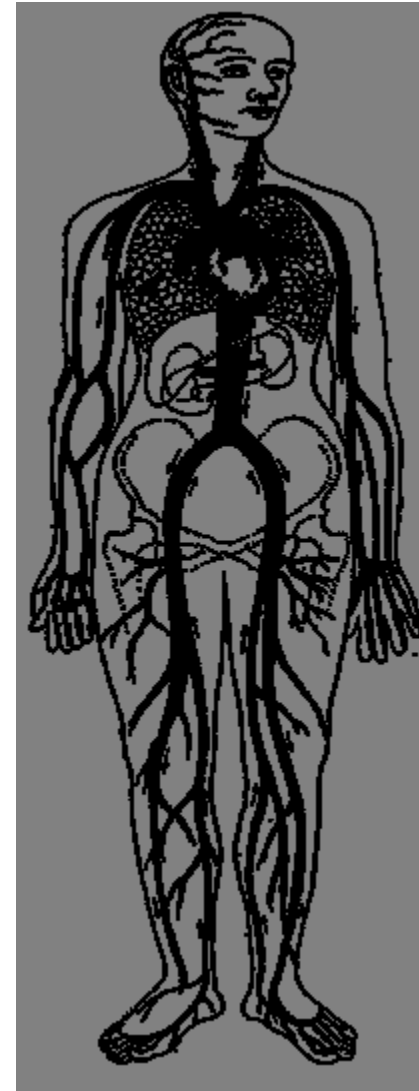


Predictions Match Observations 18 Orders of Magnitude



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

Theoretical Foundation for Allometric Scaling: Fractal Geometry



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

Allometric Theory

$$CL = CL_{std} * (WT / WT_{std})^{3/4}$$

$$V = V_{std} * (WT / WT_{std})^{4/4}$$

$$T = T_{std} * (WT / WT_{std})^{1/4}$$

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

NOTE Surface area model can be approximated by exponent of 2/3

Why Estimated Allometric Coefficients are Usually Unreliable

Table 4 Imprecision of estimates of allometric coefficient for clearance (true value 0.75)

Weight distribution	5%CI	95%CI
Log normal median 70 kg, 20%CV	0.48	1.01
Log normal median 70 kg, 50%CV	0.64	0.86
Uniform 0–140 kg	0.69	0.81

Estimation was performed using NONMEM V 1.1 with the FOCE interaction method. Empirical confidence interval (CI) and CV (standard deviation/average) from parametric bootstrap distribution of 1000 replications. One hundred subjects were drawn from each weight distribution for each replication.

Table 3 Examples that support the proposal that CL scales allometrically within humans

Drug	N	Age	Weight (kg)	Allometric coefficient	95% confidence interval	CV	Reference
Propofol	270	2–88 years	Range 12–100	0.76			(66)
Propofol	22	3–17 months	Range 8.3–12.5	0.61	0.38, 0.84	19.7%	(150)
Busulfan	24	3 months–16 years	Mean 23.8 Range 7.1–62.6	0.74	0.59, 0.90	10.7%	(45)
Phenytoin	322	18.4 SD 17.3 years 3 data sets					
		(a) 29.5 SD 15.2 years	(a) 54.4 SD 16.7	0.63	0.58, 0.67	3.7%	(63)
		(b) 6.05 SD 3.95 years	(b) 22.9 SD 11.6				
		(c) 1.33 SD 0.62 years	(c) 11.8 SD 2.07				
Oxycodone	39	6 months–7 years	Mean 16.3 Range 8–43	0.87	0.64, 1.10	13.3%	(151)
Pyrimethamine	89	1 week–14 years	Range 3–59	0.53	0.47, 0.59	5.8%	(34)
Sulfadoxine	89	1 week–14 years	Range 3–59	0.64	0.58, 0.70	4.8%	(34)
Methotrexate	49	6 months–17 years	Mean 30.56 Range 7.46–80	0.88			(152)
Valproate	225	0.1–14 years	Mean 31.3 Range 4–74	0.72	0.66, 0.77	4.2%	(153)
Sotalolol	76	0.03–17 years	Mean 16 (SD 17.1)	0.58	0.42, 0.74	14.4%	(154)

Size and Body Composition

- Fat Free Mass (FFM)
 - weight, height and sex
 - Janmahasatian et al. 2005

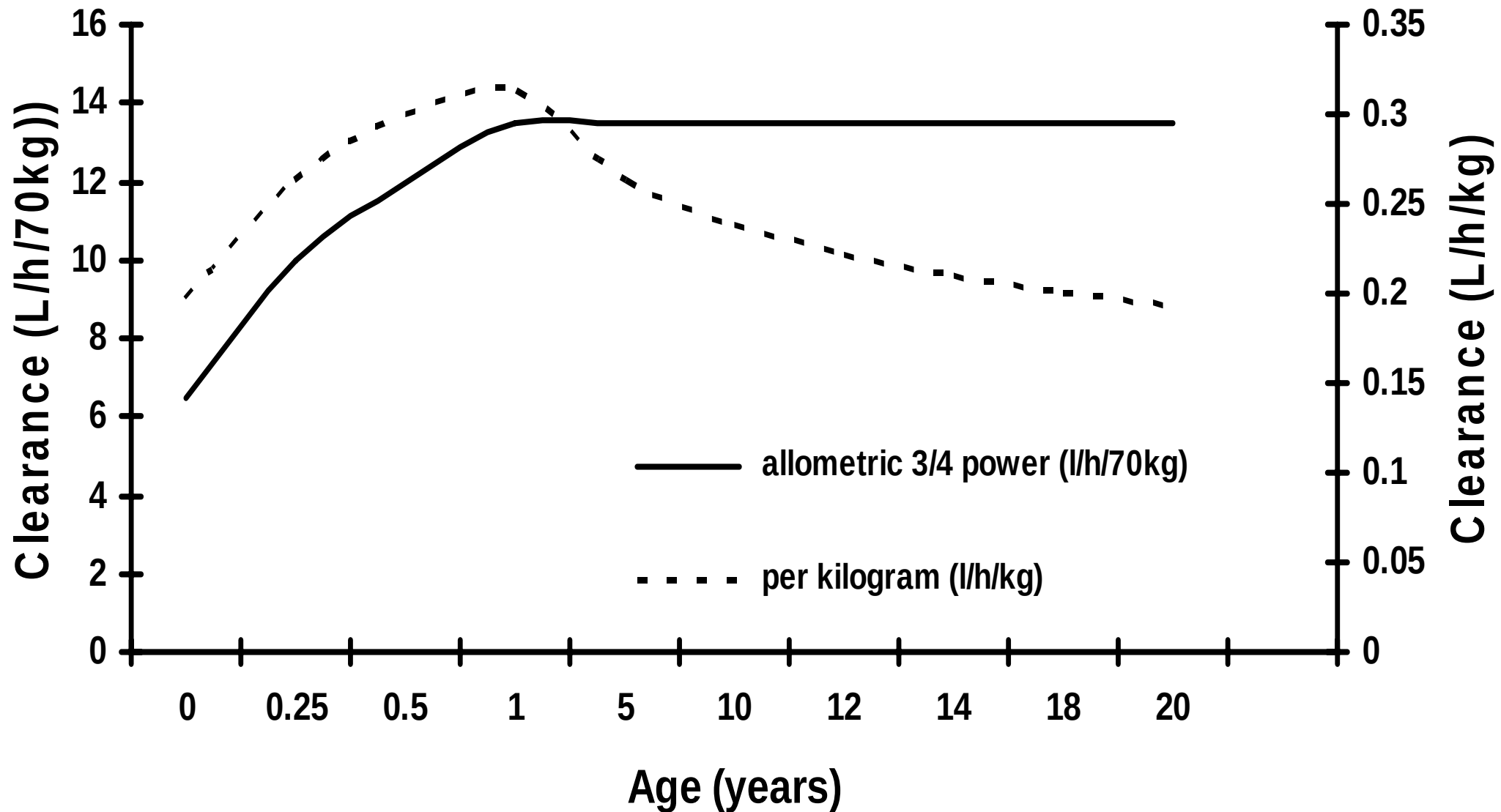
$$CL_{GRP} = CL_{STD} \cdot \left(\frac{PNWT}{WT_{STD}} \right)^{3/4} \cdot MF \cdot OF$$

- Predicted Normal Weight (PNWT)
 - FFM + Ffat*(WT – FFM)
 - Duffull et al. 2004

Janmahasatian S, Duffull SB, Ash S, Ward LC, Byrne NM, Green B. Quantification of lean bodyweight. Clin Pharmacokinet. 2005;44(10):1051-65.

Duffull SB, Dooley MJ, Green B, Poole SG, Kirkpatrick CM. A standard weight descriptor for dose adjustment in the obese patient. Clin Pharmacokinet. 2004;43(15):1167-78.

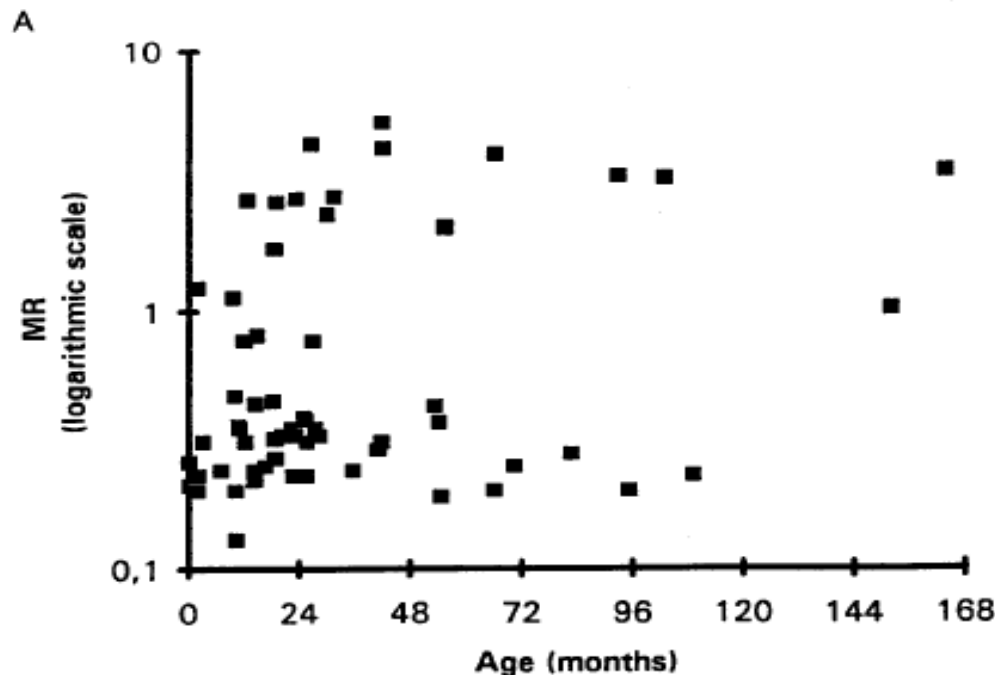
Hypothetical Drug



Maturation in Humans

N-acetyltransferase Activity Maturation With Age

Isoniazid acetylation metabolic ratio (MR) was studied in 61 children with tuberculosis after administration of isoniazid. MR was calculated as the molar acetylisoniazid to isoniazid concentration ratio. MR was used as a probe for *N*-acetyltransferase activity and to determine the acetylation phenotype. MR had a bimodal distribution with an antimode between 0.48 and 0.77. MR and the percentage of fast acetylators increased significantly with age. The cumulative frequency of fast acetylators increased with age, with a plateau reached around 4 years. MR value was checked during treatment in 44 children. All children but



Mature after 1 year or 4 years?

How to Describe Clearance Changes with Age?

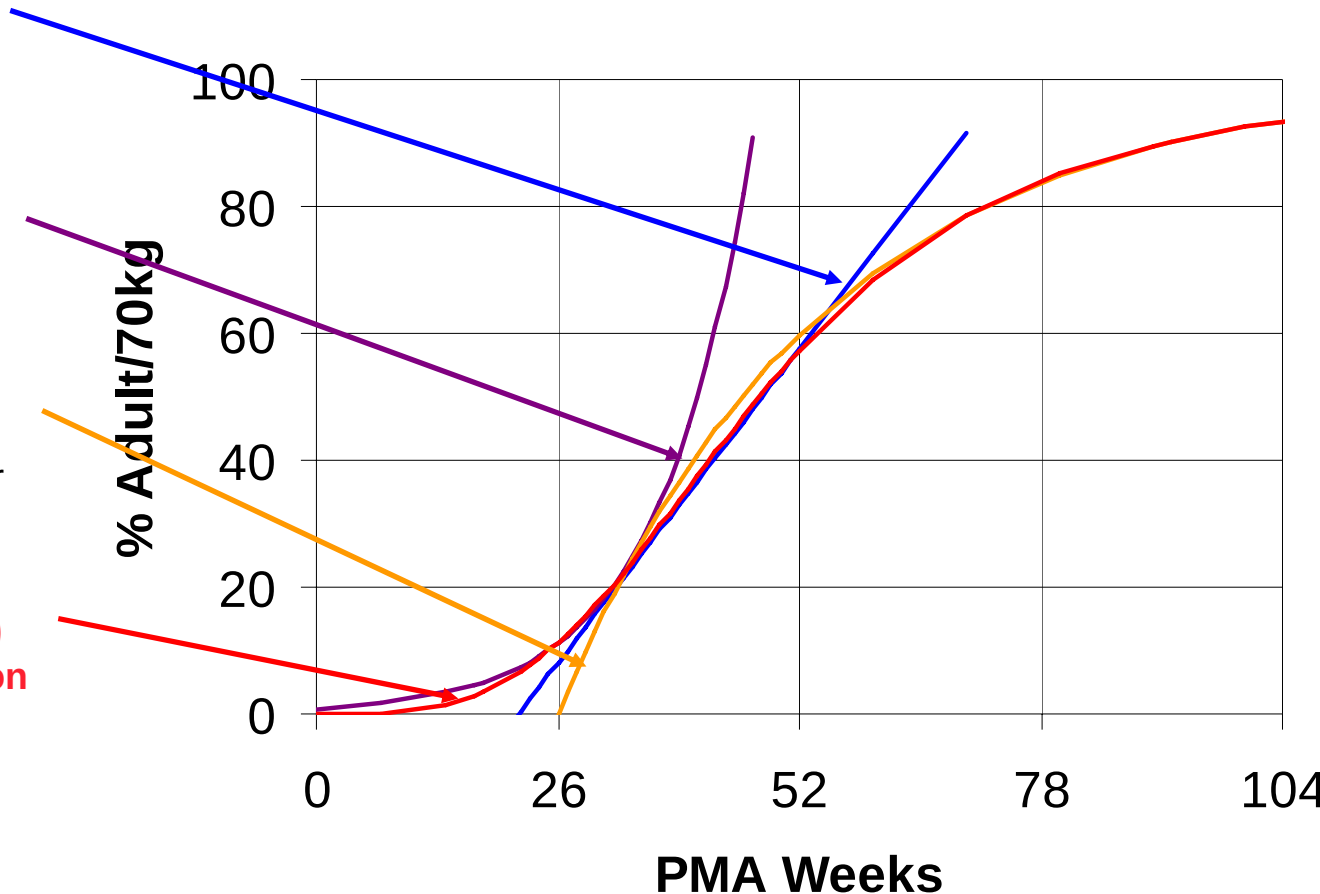
- Theory
 - Should be close to zero at conception
 - CL will appear during development in utero
 - Should reach adult values around age 20
- Observations
 - Slow changes after premature birth
 - Rapid changes around time of normal gestation
 - Slow change in older children

Which Age?

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

Maturation Models

- Linear increase (Linvall & Reith 2005)
 - OK for small age ranges e.g. premature neonates
- Exponential increase (Anderson 2000)
 - Premature and term OK but not adult values
- Asymptotic Exponential (Hayton 2002)
 - Term and adult OK but too fast for premature neonates
- **Sigmoid Emax (Tod et al. 2001)**
 - **Matches theory and observation across all ages**



$$MF = \frac{PMA^{HillCL}}{PMA^{HillCL} + TM_{50}^{HillCL}}$$

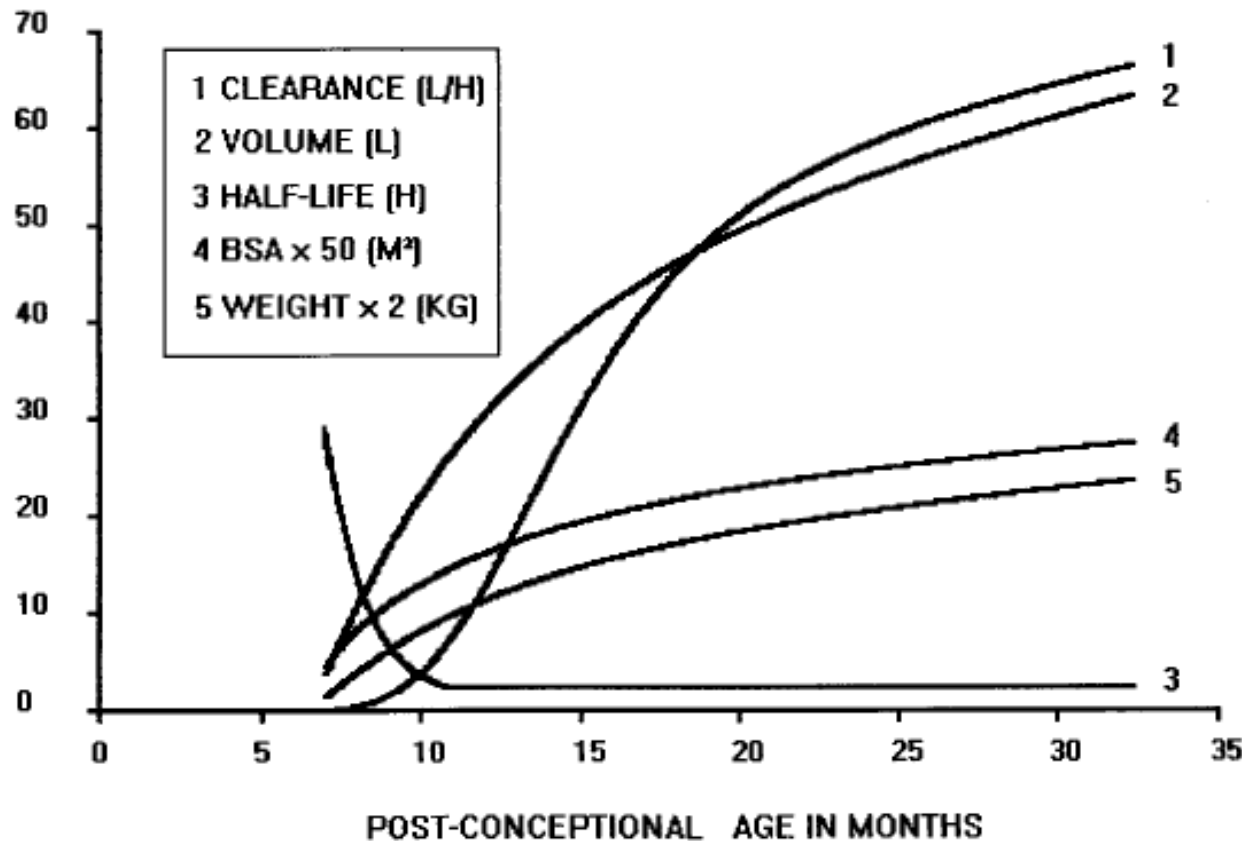
Allometry + Sigmoid Emax

$$F_{PMA} = \frac{PMA^{HillCL}}{PMA^{HillCL} + TM_{50}^{HillCL}}$$

$$CL_{WT,PMA} = CL_{STD} \cdot \frac{Wt^{3/4}}{Wt_{STD}} \cdot F_{PMA}$$

Glomerular Filtration Rate

Derived from Acyclovir in Neonates



$CL_{max}^* = 7.1 \text{ L/h/1.73 M}^2$
 $TM_{50} = 53.6 \text{ weeks PCA}$
 $Hill = 6.17$

79 subjects
0 to 2 years PNA

*=Fixed at
'normal adult value'

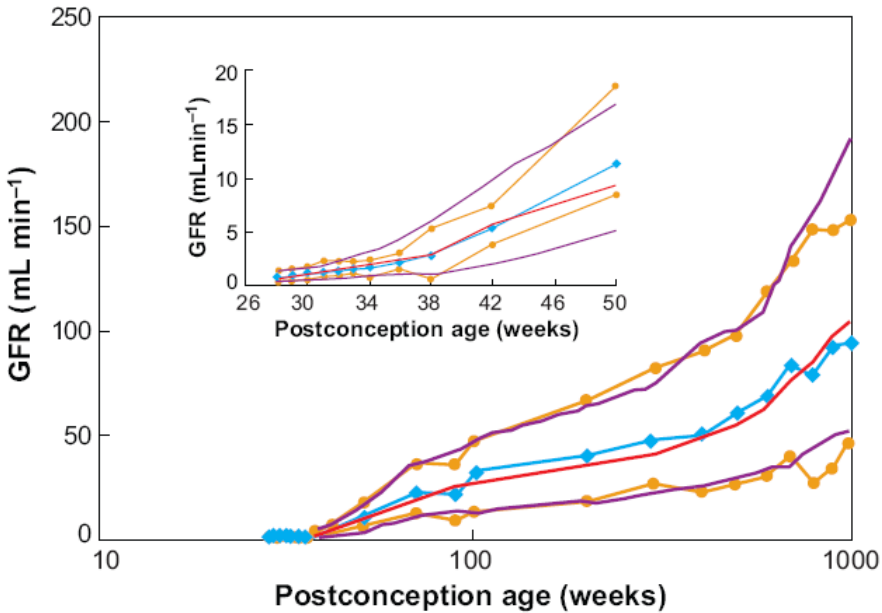
BSA model

Levetiracetam

- Antiepileptic drug
- Majority (66%) excreted unchanged in the urine
- Expect maturation of renal function to have influence
- TM_{50} 49 weeks
- Hill coefficient 2.5
- Allometric exponents estimated

Toublanc, N., Lovern, M., Sargentini-Maier, M. L., and Stockis, A. Population pharmacokinetic analysis of levetiracetam in pediatric patients with epilepsy aged 1 month to 16 years, *8th European Congress on Epileptology*, Berlin, 2008.

Median and 90% Intervals

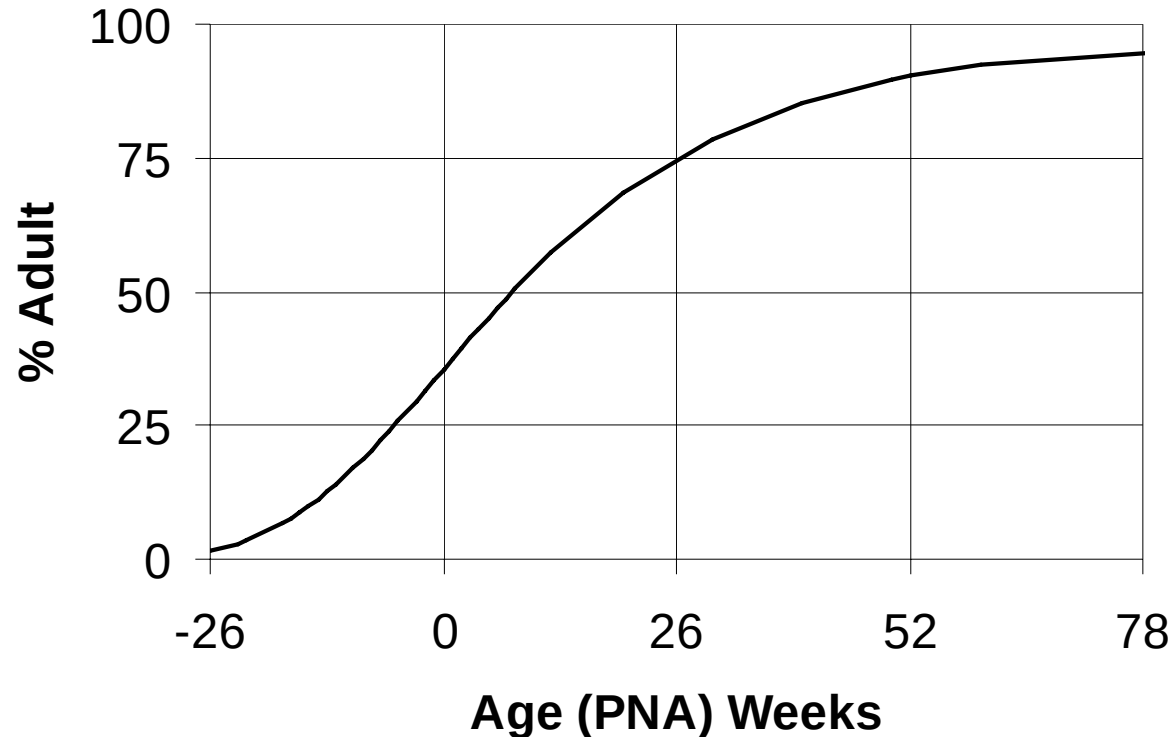


CL_{max}=6.84 L/h/70kg
 TM₅₀=46.4 weeks PCA
 Hill=3.43

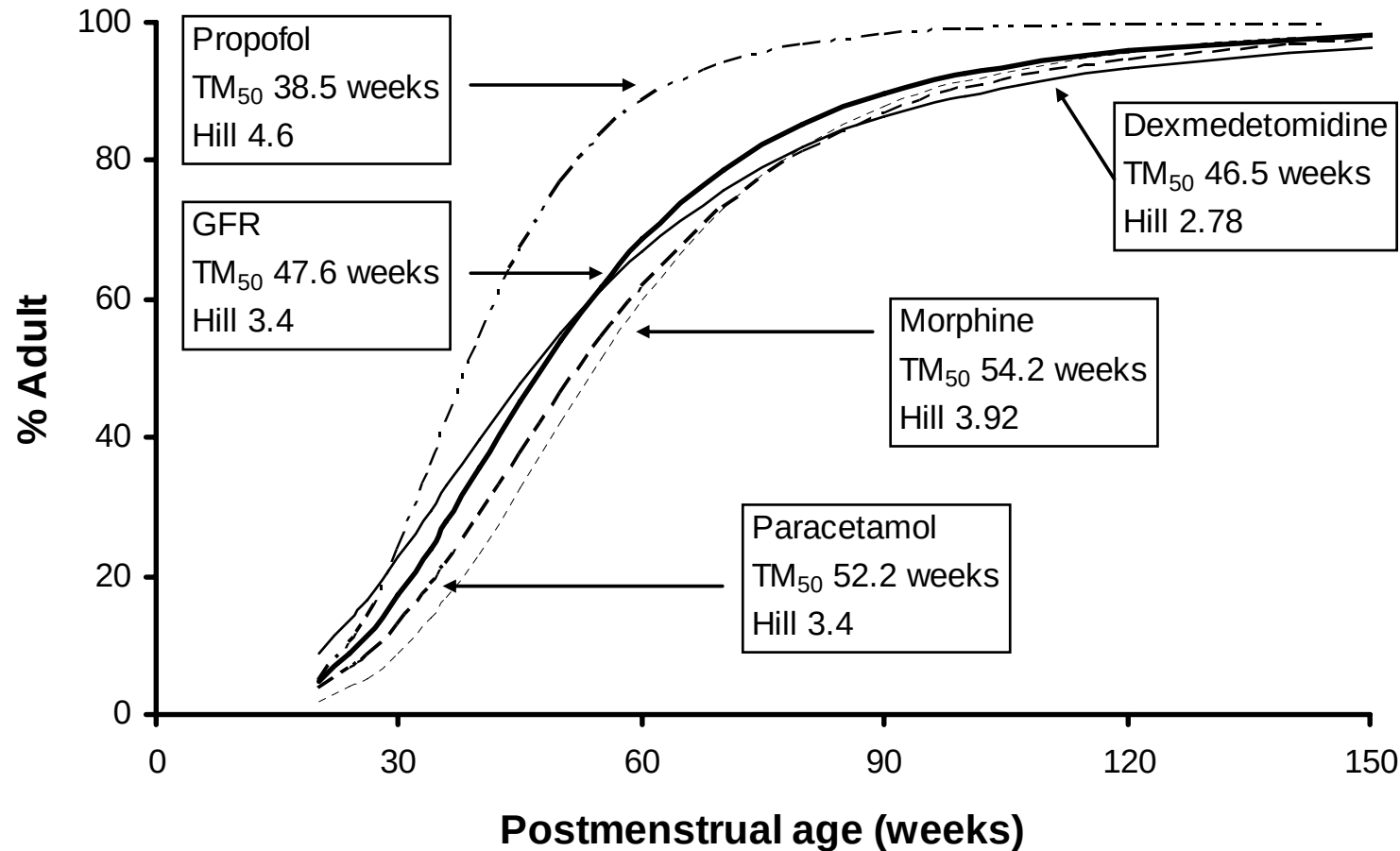
928 patients
 22 weeks PCA to 32 y

GFR Growth Curves

Rhodin MM, Anderson BJ, Peters AM, Coulthard MG, Wilkins B, Cole M, et al. Human renal function maturation – a quantitative description using weight and post-conception age. *Pediatr Nephrology* 2009



Renal and Metabolic Maturation



Propofol Metabolism
Glucuronide
CYP2B6, CYP2C9 or
CYP2A6

Accounting for Asymmetry

A

$$MF = \frac{1}{\left(1 + \delta \cdot \left[\frac{PMA}{TM_{50}} \right]^{-Hill} \right)^{1/\delta}}$$

$$MF = \frac{PMA^{Hill}}{TM_{50}^{Hill} + PMA^{Hill}}$$

$$MF = \frac{1}{\left(1 + \left[\frac{PMA}{TM_{50}} \right]^{-Hill} \right)}$$

Richards, F. J.: A flexible growth function for empirical use. *J. Exp. Bot.* 10: 290-301 (1959).

B

$$MF = \frac{1}{\left(1 + \left[\frac{PMA}{TM_{50}} \right]^{-Hill} \right)}$$

```
IF (PMA.GT.44) THEN
  HILL=HILLA
ELSE
  HILL =HILLB
ENDIF
```

Impact of Gender

- P-glycoprotein expression, CYP3A4
 - Schwartz JB. Clin Pharmacokinet 2003; 42:107-21
 - Cummins CL. Clin Pharmacol Ther 2002; 72:474-89.
- Renal Function (Cockcroft and Gault)
 - Cockcroft DW. Nephron 16:31-41

Body composition changes

- Total body water and ECF are increased in neonates
- Fat is 3% in a 1.5 kg premature neonate and 12% in a term neonate; this proportion doubles by 4-5 months of age.
- “Baby fat” is lost when infants start walking and protein mass increases (20% in a term neonate, 50% in an adult).
- Neonates have low body fat and muscle content and so less propofol is apportioned to these tissues. Delayed awakening occurs because CNS concentration remains higher than that observed in older children as a consequence of reduced redistribution.

Time for an Aphorism Change

~~Children are not Small Adults~~

Adults are BIG Children

Children are OLD Babies

THE END

