Slide 1

Quantitative Pharmacology

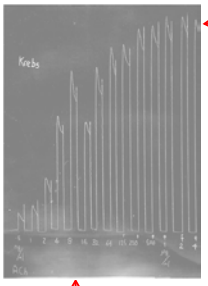
Where have we been?
Where are we going?

Nick Holford
Department of Clinical Pharmacology
University of Auckland
New Zealand

Slide 2

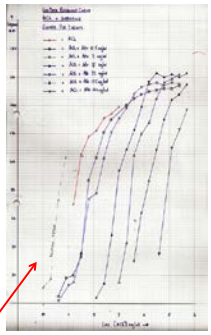
Conception

Medical Student + Guinea Pig Ileum



Emax

C50



"Dilution Error" – this is why I don't do lab work!

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Slide 3

Birth

- Hill
  - Quantitative receptor theory (+ empiricism)
- Arunlakshana & Schild
  - Competitive interaction

Hill AV. The possible effects of the aggregation of the molecules of hemoglobin on its dissociation curves. J Physiol (Lond) 1910; 40: iv-vii.

Arunlakshana O, Schild HO. Some quantitative uses of drug antagonists. Br J Pharmacol Chemother 1959; 14: 48-58.

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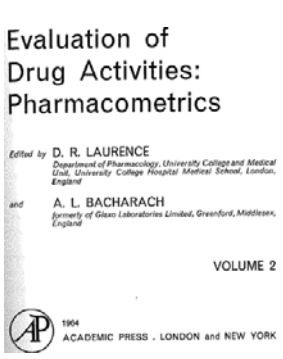
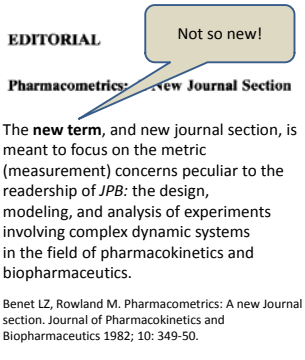
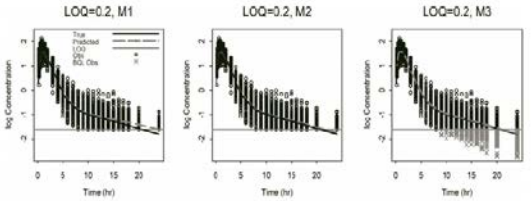
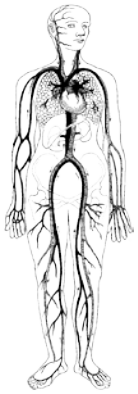
Slide 4	**Childhood** • Holford & Sheiner – Understanding the concentration-effect relationship • Stanski, Weiss, Levy – Delayed drug effects – Distribution, binding, turnover ©NHG Holford, 2012, all rights reserved.	
Slide 5	**Teenage Girl meets Boy** Variable PK meets PD • Sheiner & Beal 1978 – The population approach • Tanigawara 1997 – Bridging with the world ©NHG Holford, 2012, all rights reserved.	
Slide 6	**Origin of Pharmacometrics**  Evaluation of Drug Activities: Pharmacometrics Edited by D. R. LAURENCE Department of Pharmacology, University College and Medical Unit, University College Hospital Medical School, London, England and A. L. BACHARACH formerly of Glaxo Laboratories Limited, Greenford, Middlesex, England VOLUME 2 1964 ACADEMIC PRESS . LONDON and NEW YORK  EDITORIAL Not so new! Pharmacometrics: A New Journal Section The **new term**, and new journal section, is meant to focus on the metric (measurement) concerns peculiar to the readership of *JPB:* the design, modeling, and analysis of experiments involving complex dynamic systems in the field of pharmacokinetics and biopharmaceutics. Benet LZ, Rowland M. Pharmacometrics: A new Journal section. Journal of Pharmacokinetics and Biopharmaceutics 1982; 10: 349-50. ©NHG Holford, 2012, all rights reserved.	On 25/03/2010 12:47 p.m., malcolm rowland wrote: “Although I had left UCSF in 1975, in the late 70's Lewis and I got together and decided to organise a workshop which as you will probably recall was first run in the UK Lake District in 1981. During the run up to this first workshop Lewis and I spent a lot of time discussing various topics and during the 1981 workshop itself, he indicated that he would like to get more involved in the journal. As Les indicated we discussed this and made the proposition to Lewis to be a section editor, and as I recall it was he who suggested the title of pharmacometrics. I certainly was unaware that it had been used by Lawrence some 20 years previously. Les and I then wrote the editorial. And, yes, it did have a marketing slant. But as Les has rightly told me on several occasions, language is a living subject and the meaning of words is continuously changing, sometimes minimally, sometimes substantially.”

Slide 7	**Maturation** • Tools – NONLIN -> WinNonLin – NONMEM -> NM-TRAN – Clinical Trial Simulator • Communities – nmusers and pharmpk – PAGE, PAGANZ, PAGJA, PAGK, PAGIN, ACoP, WCoP – ISoP ©NHG Holford, 2012, all rights reserved.	
Slide 8	**Adult Topics** • *What are the lessons we still have not learned properly?* • *What are the important factors determining dose?* • *How can PKPD help drug development?* • *How can pharmacometrics help patients?* ©NHG Holford, 2012, all rights reserved.	
Slide 9	***Encouraging better use of drug concentration measurements in the laboratory*** • Chemical analysts continue to **report measured concentrations as being below the limit of quantitation** (BLQ) when the value is less than the lower limit of quantitation. • Providing BLQ values rather than the actual measurement causes **bias in the estimation of pharmacokinetic parameters** and may lead to selection of an **inappropriate model**. • Chemical analysts should be encouraged to help pharmacokinetic analyses by **reporting what they measure** and not censor the data by **inappropriate application of guidelines** for validation of assay methodologies ©NHG Holford, 2012, all rights reserved.	

Slide 10	**We don't need this if chemical analysts are honest**  "If the times of the BQL observations are not available, then adjusting the likelihoods for the remaining data (M2) may improve parameter estimates compared to no adjustment (M1)." "In most cases, the time when the BQL observations occur are recorded and a better approach for handling BQL data would be treating them as censored observation (M3)." Ahn JE, Karlsson MO, Dunne A, Ludden TM. Likelihood based approaches to handling data below the quantification limit using NONMEM VI. J Pharmacokinet Pharmacodyn. 2008;35(4):401-21. ©NHG Holford, 2012, all rights reserved.	
Slide 11	***Understanding that Area under Curve, Tmax and Cmax are not pharmacokinetic parameters*** • **Naïve descriptions** of the time course of drug concentration are reported in terms of area under the curve, peak measured concentration and time to peak concentration. • These are **pharmacokinetic statistics** but they are not pharmacokinetic parameters. • **They are not parameters** because they depend on the dose and on the design of the study. ©NHG Holford, 2012, all rights reserved.	
Slide 12	**Time for ADME to be Forgotten** **Pharmacokinetic Models (IDO)** [edit] Pharmacokinetics is a science that studies the key processes of input, distribution and output of drugs from living organisms. Input processes describe controlled administration (e.g. IV infusion) and absorption from a depot (e.g. oral dosing). Output includes metabolism to another molecule (e.g. by cytochrome enzymes) and excretion as unchanged molecule (e.g. in the urine). Older descriptions of PK refer to ADME (absorption, distribution, metabolism, excretion) but this 4 component classification does not properly include drug input that is not absorption and unnecessarily splits output into metabolism and excretion. Pharmacokinetic models are created by combining models for input, distribution and output (IDO). http://www.mashframe.com/isop_wiki ©NHG Holford, 2012, all rights reserved.	

Slide 13	**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**. ©NHG Holford, 2012, all rights reserved.	
Slide 14	Theoretical Foundation for Allometric Scaling    $CL_{CHILD} = CL_{ADULT} \cdot \left(\frac{WT_{CHILD}}{WT_{ADULT}}\right)^{3/4}$ West GB, Brown JH, Enquist BJ. The fourth dimension of life: fractal geometry and allometric scaling of organisms. Science. 1999;284(5420):1677-9. ©NHG Holford, 2012, all rights reserved.	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 to support the delivery system as well as the target cells. This leads to the theoretical allometric scaling function with a power of ¾.
Slide 15	Estimation of Allometric Exponent 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. Don't do it unless you know you can account for all other size associated factors and have the right distribution of weights! ©NHG Holford, 2012, all rights reserved.	

Slide 16

Standard Weight for Allometric Models

Concern is expressed sometimes that scaling parameter values estimated in neonates and children in terms of an adult size standard of 70 kg may bias the estimates or affect the precision of estimation. There is no basis for this concern. This can be seen by inspection of the allometric covariate model which may be re-arranged:

$$Fsize = (W)^{3/4} \cdot \left(1/70\right)^{3/4}$$

The expression

$$\left(1/70\right)^{3/4}$$

is simply a constant that is determined by whatever weight is chosen for standardization. The precision of a parameter estimate will not be changed by multiplying the parameter value by an ad hoc constant.

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Slide 17

Renal function *and* ***post-menstrual age*** *are the next most important determinants of drug dose*

- **Differences in renal function** can explain about a **10 fold difference in total drug clearance**. 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, Anderson et al. 2009).
- **Maturational changes** of **10 fold** have been observed for drug clearances. Age in older adults has a minor influence on drug clearance (once weight and other factors such as renal function are accounted for).

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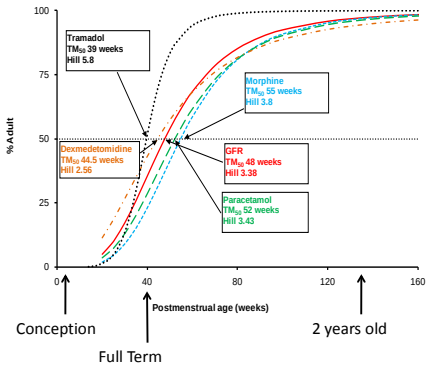
Slide 18

Clearance Maturation



Maturation is complete by 2 years of age –

– then weight is the sole predictive factor for drug clearance

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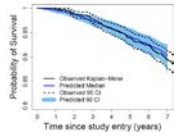
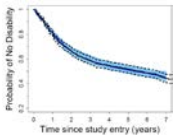
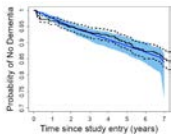
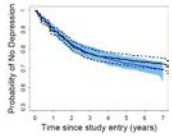
Slide 19	*Body size, renal function and post-menstrual age are the most important determinants of drug dose* • In comparison to these factors other covariates such as **genotype often pale into insignificance**. • Quantitative pharmacology can help put the role of using covariates to predict drug dose into **a realistic perspective**. ©NHG Holford, 2012, all rights reserved.	
Slide 20	*Drug Development - Linking PKPD and disease progress to clinical outcome* • PKPD models are usually based on biomarkers that are **not directly connected** to patient symptoms or improvement in function or survival. • It is only recently that methodology has been developed and applied to biomarker based PKPD which can be used to understand and **predict clinical outcome**. • These quantitative links between the time course of biomarkers and the time to a clinical event represent **the next step forward** for understanding and predicting clinical pharmacology. ©NHG Holford, 2012, all rights reserved.	
Slide 21	PKPD Predicts Outcome Death  Disability  Cognitive Impairment  Depression  Vu, T. C., J. G. Nutt, et al. (2012). "Disease progress and response to treatment as predictors of survival, disability, cognitive impairment and depression in Parkinson's disease." British Journal of Clinical Pharmacology **74**(2): 284-295.	

Slide 22

Making the most of drug concentration measurements at the bedside

- Measurements of drug response after starting treatment e.g. international normalized ratio or drug concentrations, have long been held out as a method for **dose individualization that goes beyond the use of covariates** such as weight, renal function and age.

- Therapeutic drug monitoring is involved with measurement of drug concentrations but the link between the measurement and individualization of dose **requires more than just comparing the concentration to a therapeutic range**.

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Slide 23

Making the most of drug concentration bedside

- Despite a **clear demonstration of improved survival** in acute lymphoblastic leukemia when methotrexate doses are based on **Bayesian predictions of clearance**, this breakthrough in treatment of the disease is still rarely used because of the perceived **difficulties of interpretation of the concentrations**.

- The widespread availability of access to **computational resources on the internet** opens up the possibility of making Bayesian methodologies available at the bedside to any clinician with a smartphone.

Evans, W. E., M. V. Relling, et al. (1998). "Conventional compared with individualized chemotherapy for childhood acute lymphoblastic leukemia." N Engl J Med **338**(8): 499-505.

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Slide 24

The Birth of Clinical Pharmacometrics

Comput Biomed Res 1969; 2: 507-18.

Computer-Aided Long-Term Anticoagulation Therapy

LEWIS B. SHEINER *

Division of Computer Research and Technology, National Institutes of Health, Public Health Service, Department of Health, Education, and Welfare, Bethesda, Maryland 20014

$$dF/dt = -k(2)F + (1 - sD)\,k(3), \quad \text{for } 1 - sD > 0,\ F < 1 \text{ and}$$
$$dF/dt = -k(2)F, \quad \text{for } 1 - sD < 0 \text{ or whenever } F = 1,$$

where F is the "clotting factor" level, dF/dt is the rate of change of F with time, $k(2)$ is the rate constant for the decay of F, D is the drug level (substitute the equations for D, above), $k(3)$ is the normal maximal synthesis rate of the clotting factor and s is a "sensitivity factor" relating a given drug level to its effect on synthesis.

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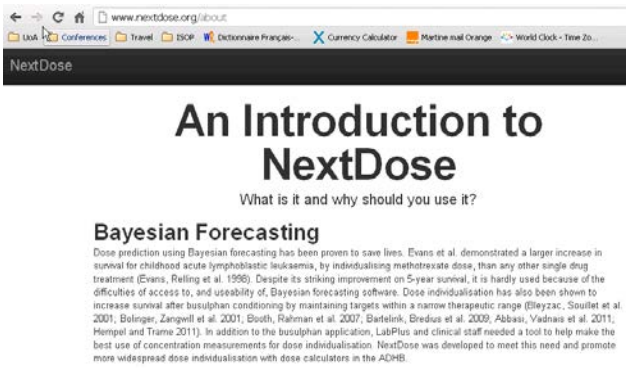
Slide 25	**Clinical Pharmacometrics Today**  Holford, S. D. et al. (2012). "NextDose - A web based collaborative tool for dose individualisation." PAGANZ http://www.paganz.org/abstract/1295 ©NHG Holford, 2012, all rights reserved.	
Slide 26	ISOP **What Next?** http://www.go-isop.org •JOIN •VOLUNTEER •ATTEND •LEARN •EXPLORE •DONATE ©NHG Holford, 2012, all rights reserved.	