ANIMAL SCALE UP

Robert L. Dedrick, Ph.D.
Chief, Drug Delivery and Kinetics Resource, NIH

SUMMARY

Despite the influence of allometry on the development of biology and an underlying belief that experimental systems provide useful information about humans, disproportionate emphasis has been placed on species differences. This would appear to derive from the culture of biology because differences among species have often been more interesting than similarities and because these differences can provide important information on the development of species. We recognize that no other animal is the same as a human in any general biological sense and that insistence on "sameness" in a model system is illusory. I would propose that we adopt more of an engineering-design view when we develop experimental systems in pharmacokinetics and attempt to use data from these systems for predictive purposes. If we do this, it is axiomatic in biology as in engineering that the model system is never the same as the prototype. Interpretation is always required. In some simple systems, concepts of similitude place design on a sound theoretical basis. But in more complex situations rigorous similitude may not be attainable. In these cases it is often possible to model parts of a complex system and use model-dependent information in a design process which incorporates sound theoretical principles but often contains judgment and experience as well. This approach is illustrated by an examination of the use of experimental *in-vitro* and *in-vivo* data to predict pharmacokinetics of drugs in humans.

ALLOMETRIC EQUATIONS

It has been observed that many physiological processes and organ sizes show a relatively simple power-law relationship with body weight when these are compared among mammals. The well known allometric equation is

$$P = a(BW)^m \qquad (1)$$

where P = physiological property or anatomic size
a = empirical coefficient
BW = body weight
m = allometric exponent

Note that a is not dimensionless; its value depends on the units in which P and BW are measured, while the exponent, m, is independent of the system of units. Note further that if m = 1, then P is proportional to BW. If m<1, P increases less rapidly than BW. If m>1, P increases more rapidly that BW. Dividing both sides of Eq (1) by BW shows that

$$\frac{P}{BW} = a(BW)^{m-1} \qquad (2)$$

Thus, if the allometric exponent is less than unity, as observed for many measures of physiologic function such as basal oxygen consumption and creatinine clearance, the function per unit of body weight decreases as body weight increases. If m = 0.7 for the renal clearance of a particular drug, the clearance per unit body weight in a 20-g mouse would expected to be $[(70{,}000)/(20)]^{0.3}$ = 12 times that in 70-kg human. If the volume of distribution is similar between the two species (such as body water) and the drug is cleared only by the kidney, then as a rough approximation pharmacokinetics would be occurring 12-times faster in the mouse. One hr in a mouse would be pharmacokinetically equivalent to 12 hr in a human. Such considerations are important in the design of drug studies, because pharmacokinetic time scales vary greatly among species.

PHYSIOLOGICAL PHARMACOKINTICS

The distribution and disposition of a drug in the body result from a complex set of physiological processes and biochemical interactions. In principle it is possible to describe these processes and interactions in mathematical terms and, if sufficient data are available, to predict the time course of drug and metabolite(s) in specific anatomic sites.

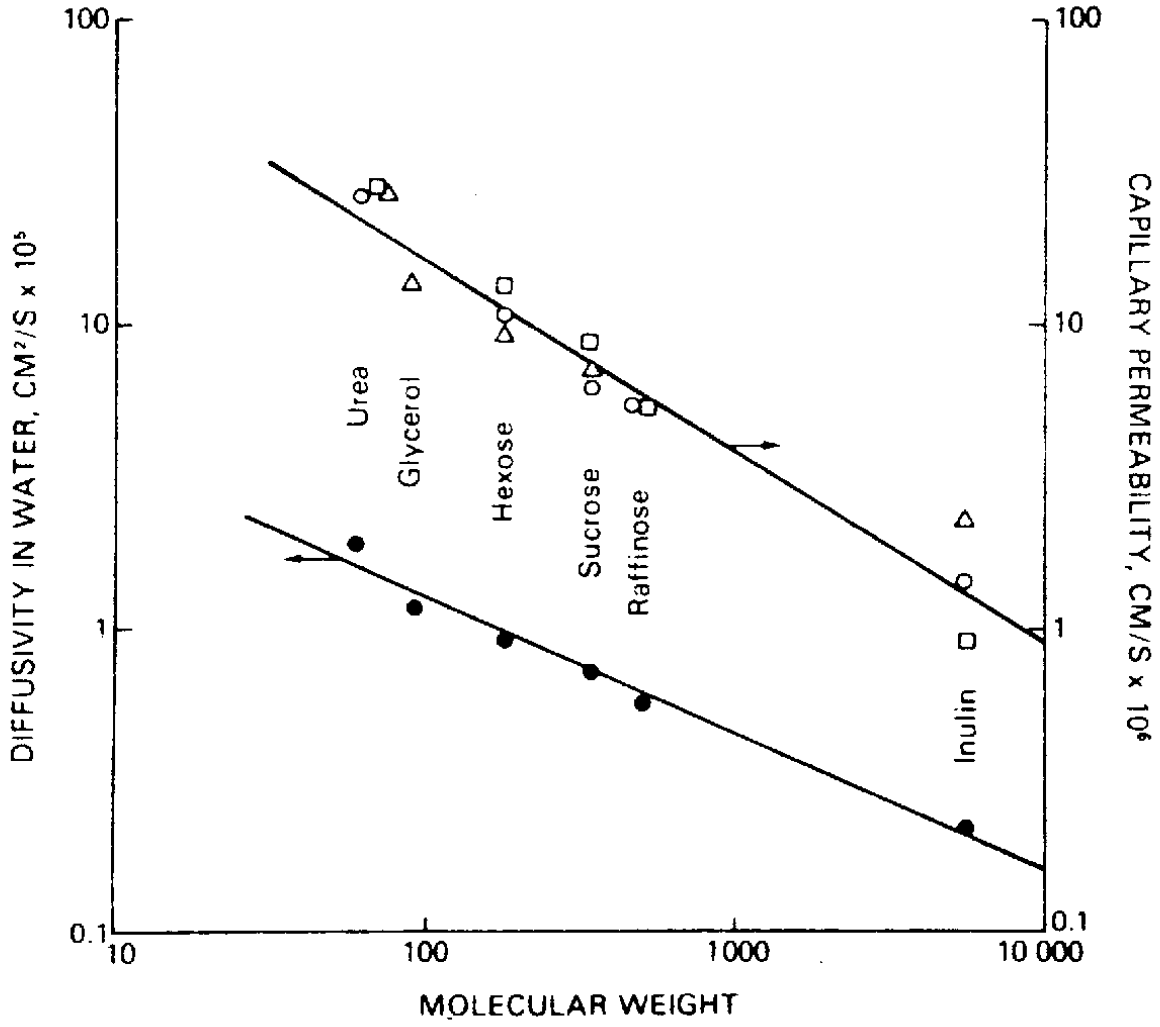
The basis of a physiological pharmacokinetic model is a flow diagram showing the anatomic relationships among the various organs and tissues. The accumulation of a drug within a compartment is described by an appropriate mass-balance equation. As an illustration, we consider the accumulation of a drug in the kidney, which is assumed both to metabolize the drug by a saturable process and to clear it by filtration and possibly secretion. It is further assumed that the concentration within the compartment is uniform and equal to that of venous blood.

$$V_K \frac{dC_K}{dt} = Q_K C_B - Q_K C_K - CL_K C_B - \left[\frac{v_{max,K} C_K}{K_{m,K} + C_K}\right] V_K \qquad (3)$$

where V = compartment volume, ml
C = drug concentration, µg/ml
t = time, min
Q = blood flow rate, ml/min
v_{max} = maximum rate of metabolism, µg/(min ml)
K = Michaelis constant, µg/ml
CL = non-metabolic clearance, ml/min
and the subscripts K and B refer to kidney and arterial blood, respectively.

Similar equations can be written for all relevant compartments. If parameters are chosen, the resulting set of ordinary differential equations can be solved numerically to yield predictions of the concentration of the drug and metabolite(s) in each of the compartments as a function of time. Of course, the simplifying assumptions above can be relaxed to include much more detail concerning plasma and tissue binding, transport at

the level of the blood capillary and cell membrane, and spatial nonuniformity – but at the cost of increasing complexity and the requirement for more parameters.



Capillary permeability and aqueous diffusivity of hydrophilic solutes versus molecular weight. Key: (○) *cat leg;* (□) *human forearm;* (△) *dog heart;* (●) *diffusivity*

Dedrick RL et al, ASAIO J 5:1-8, 1982

ALLOMETRIC EQUATION

$$P = a(BW)^m$$

where P = physiological property or anatomic size
a = empirical coefficient
BW = body weight
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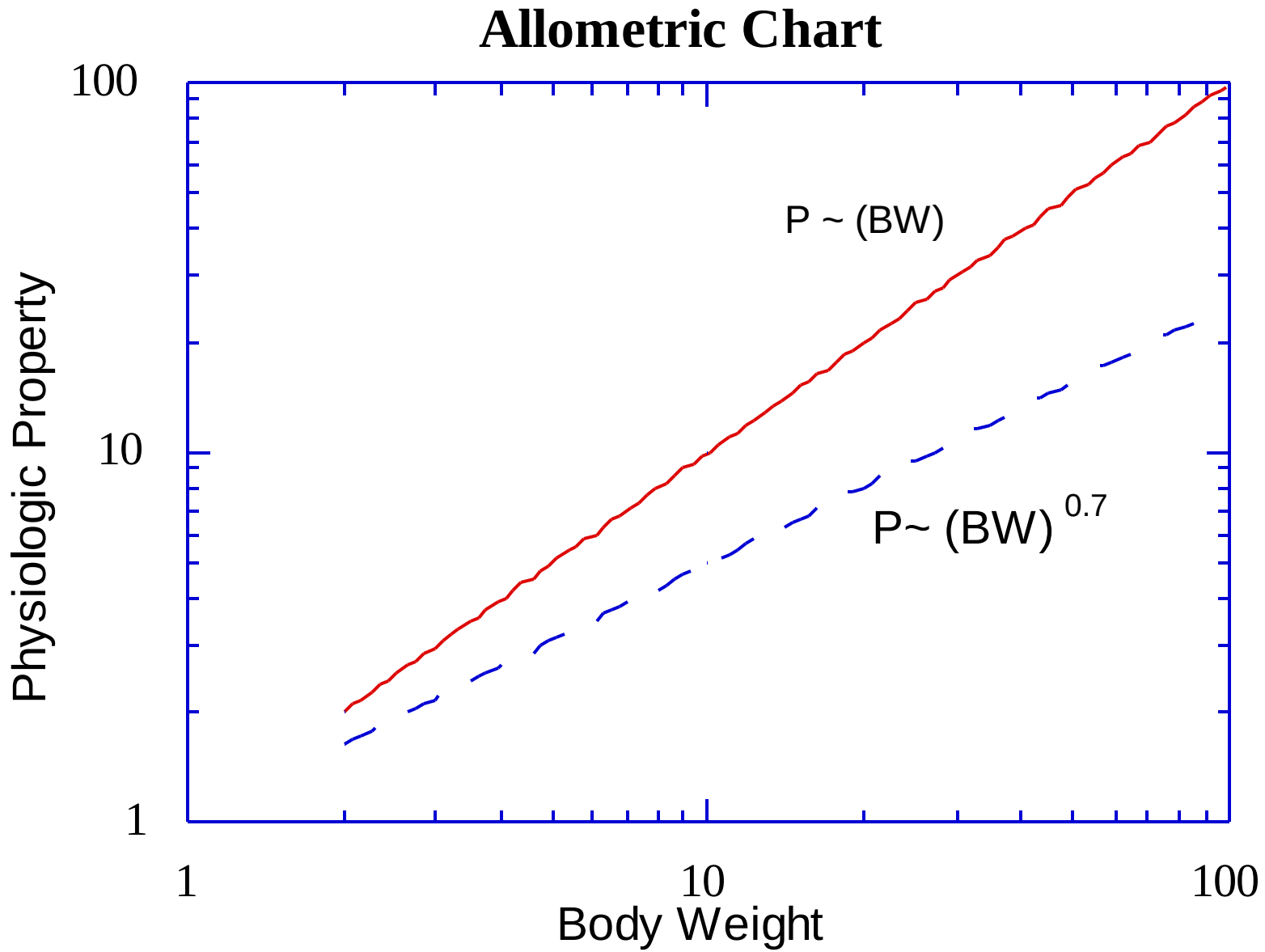
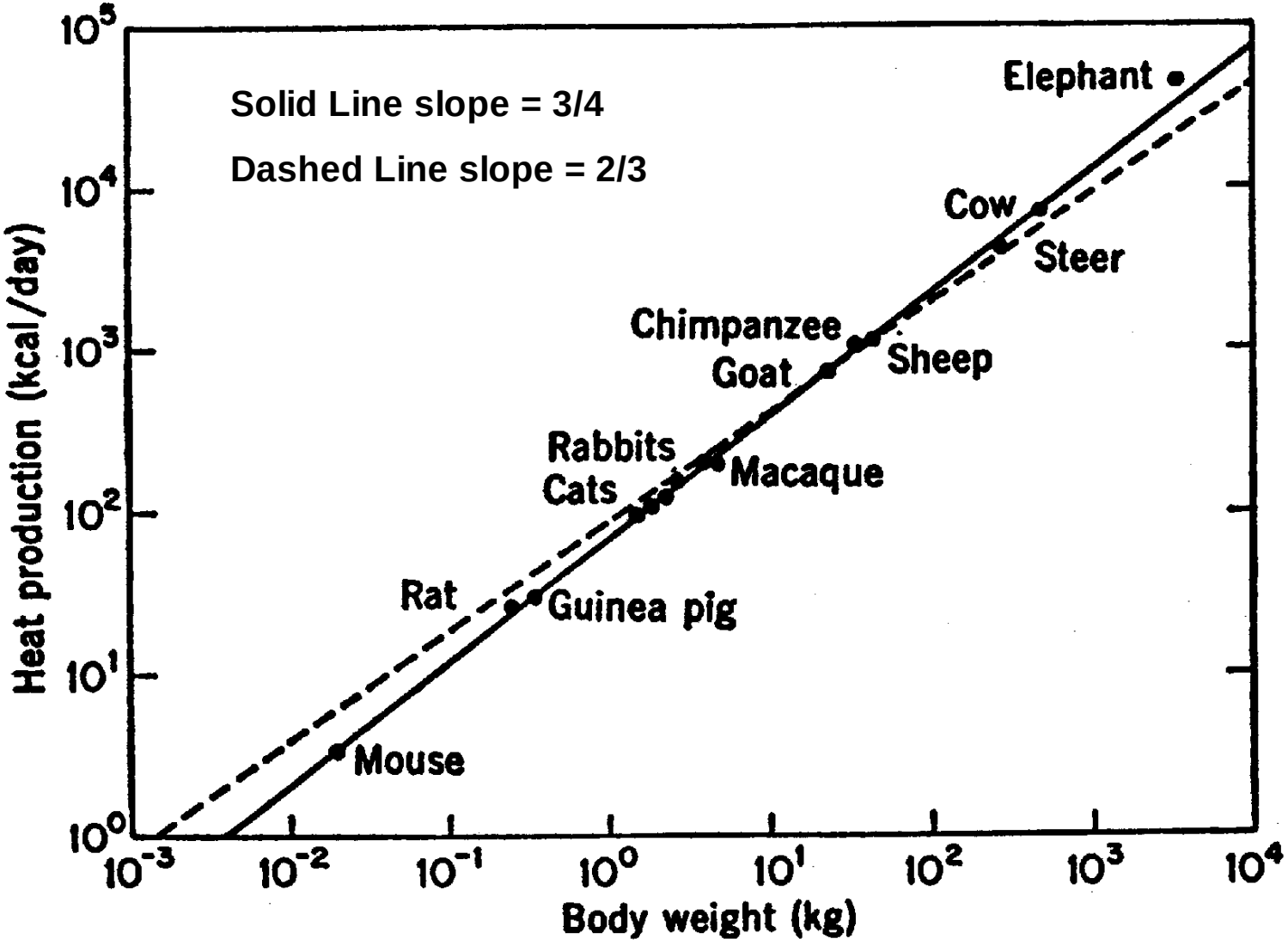
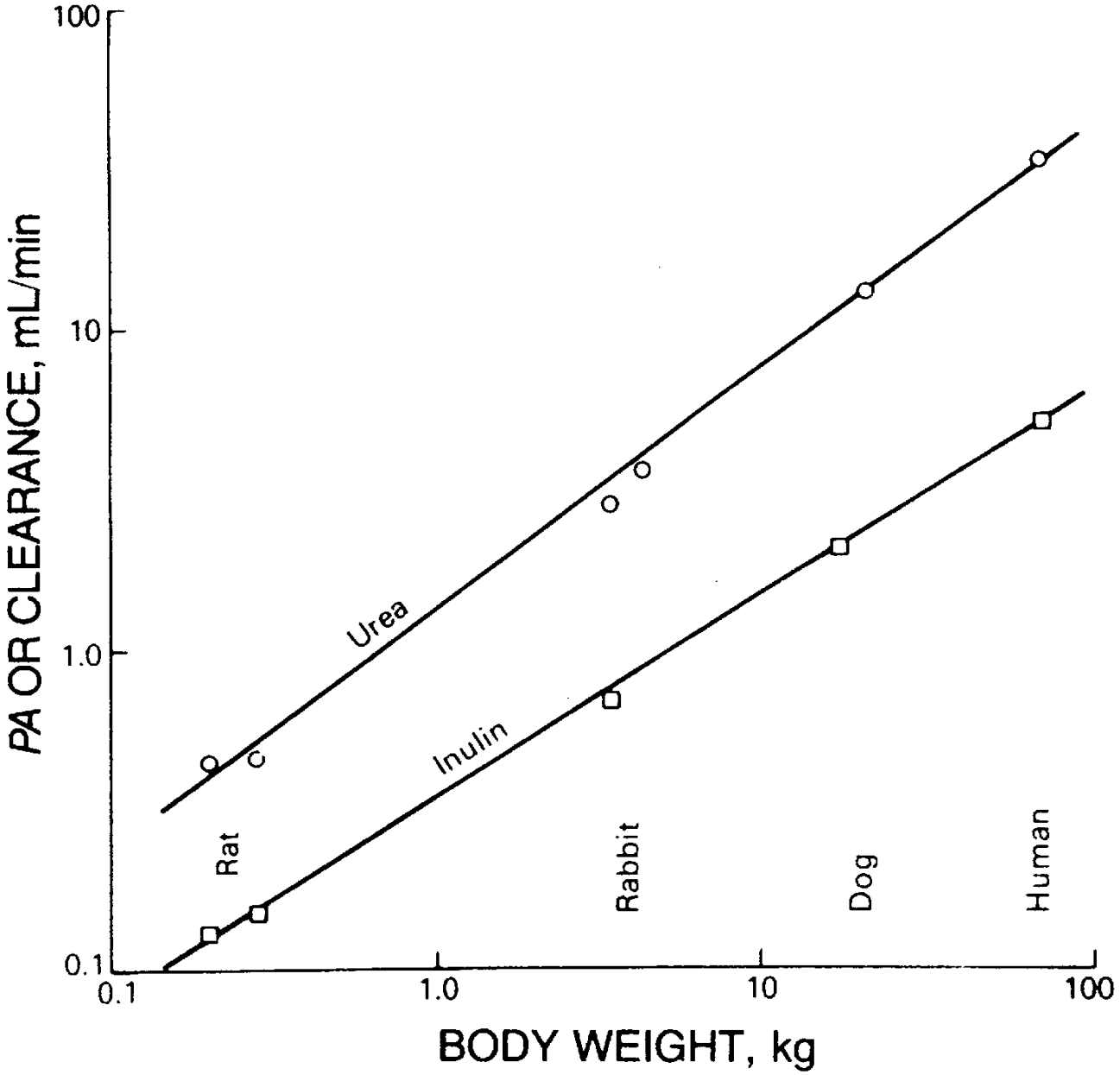
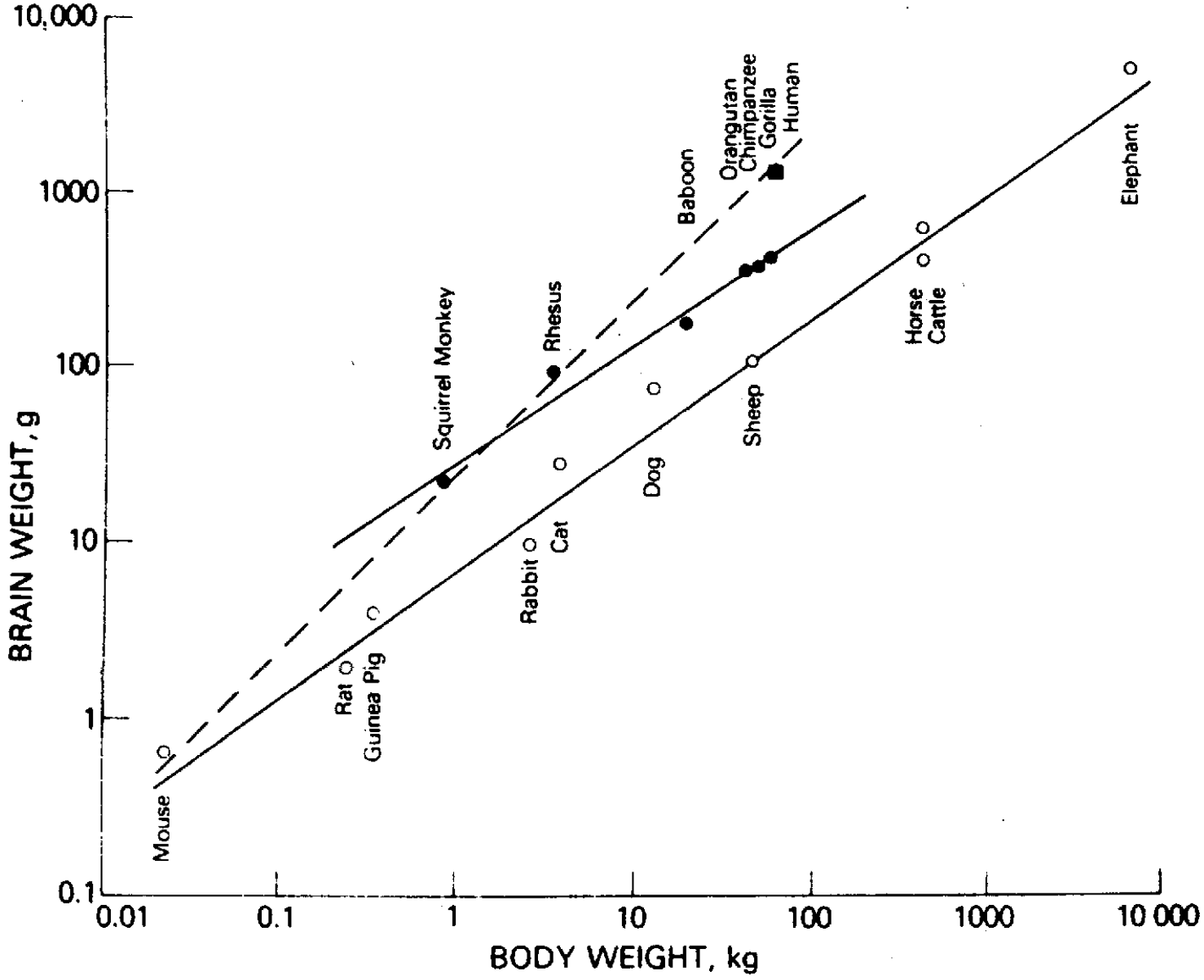

Allometric Chart
100
10
1
Physiologic Property
P ~ (BW)
P~ (BW) 0.7
1
10
100
Body Weight



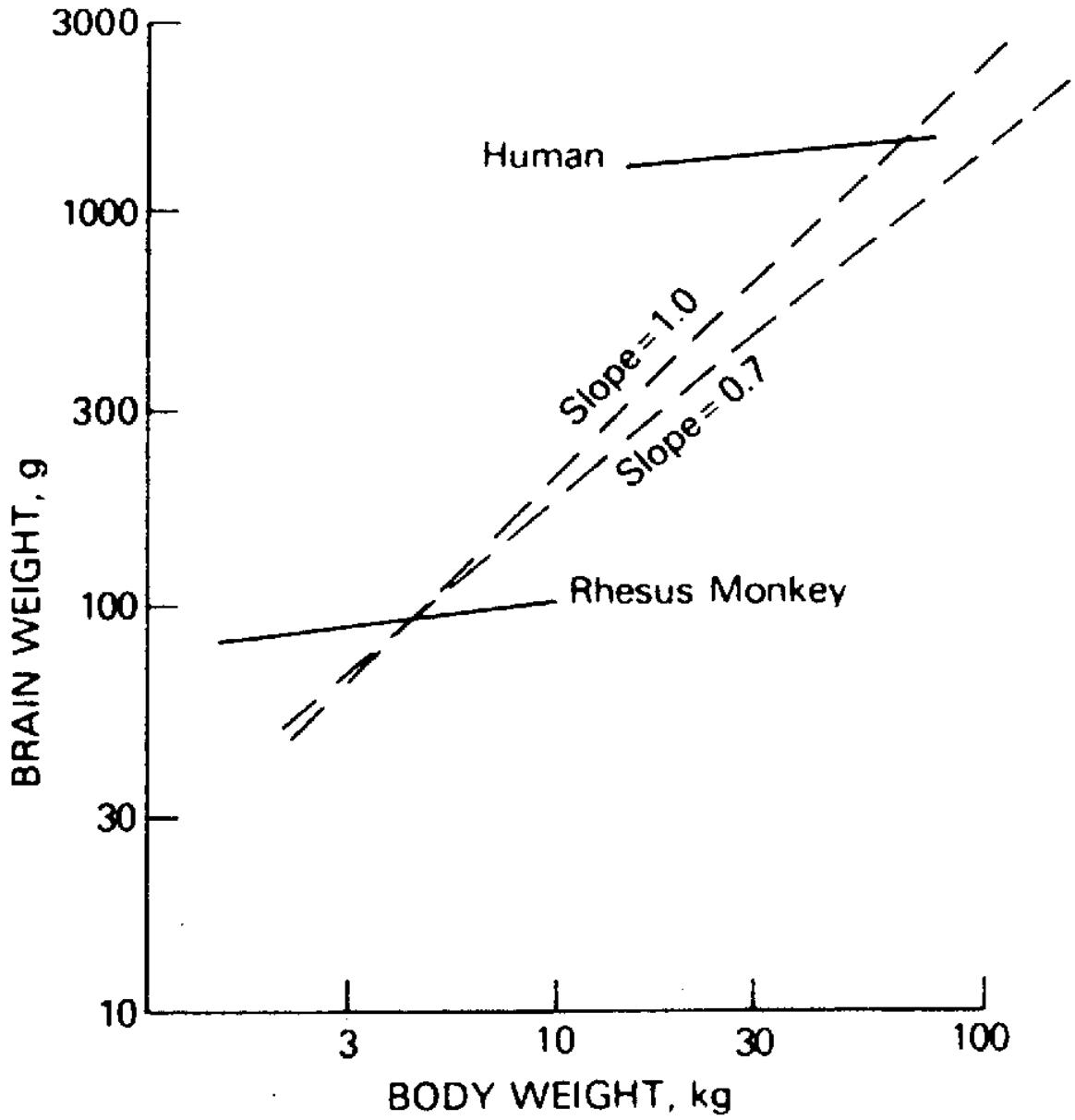
McMahon T. Science 179:1201-1204, 1973



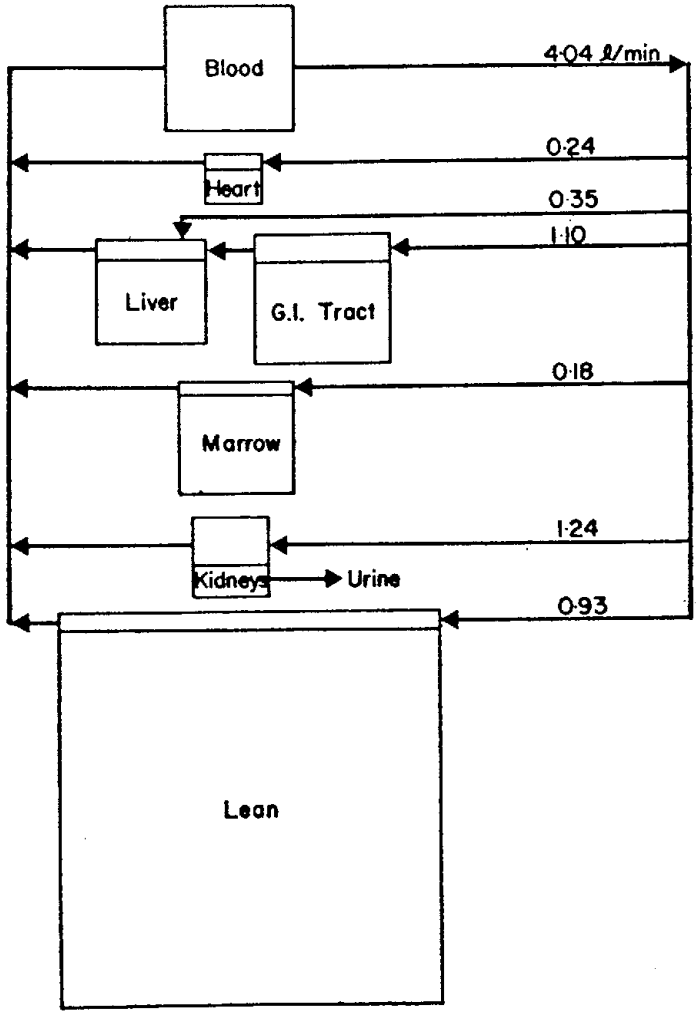
Dedrick RL et al, ASAIO J 5:1-8, 1982



Dedrick RL et al, Cancer Treat Rep 68:373-380, 1984



Dedrick et al, Cancer Treat Rep 68:373-380, 1984



Compartmental Model for Ara-C Pharmacokinetics

Dedrick RL et al, Biochem Pharmacol 21:1-16, 1972

MASS BALANCE EQUATION

$$V_K \frac{dC_K}{dt} = Q_K C_B - Q_K C_K - CL_K C_B - \left(\frac{v_{max,K} C_K}{K_{m,K} + C_K} \right) V_K$$

where V = compartment volume, ml
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t = time, min
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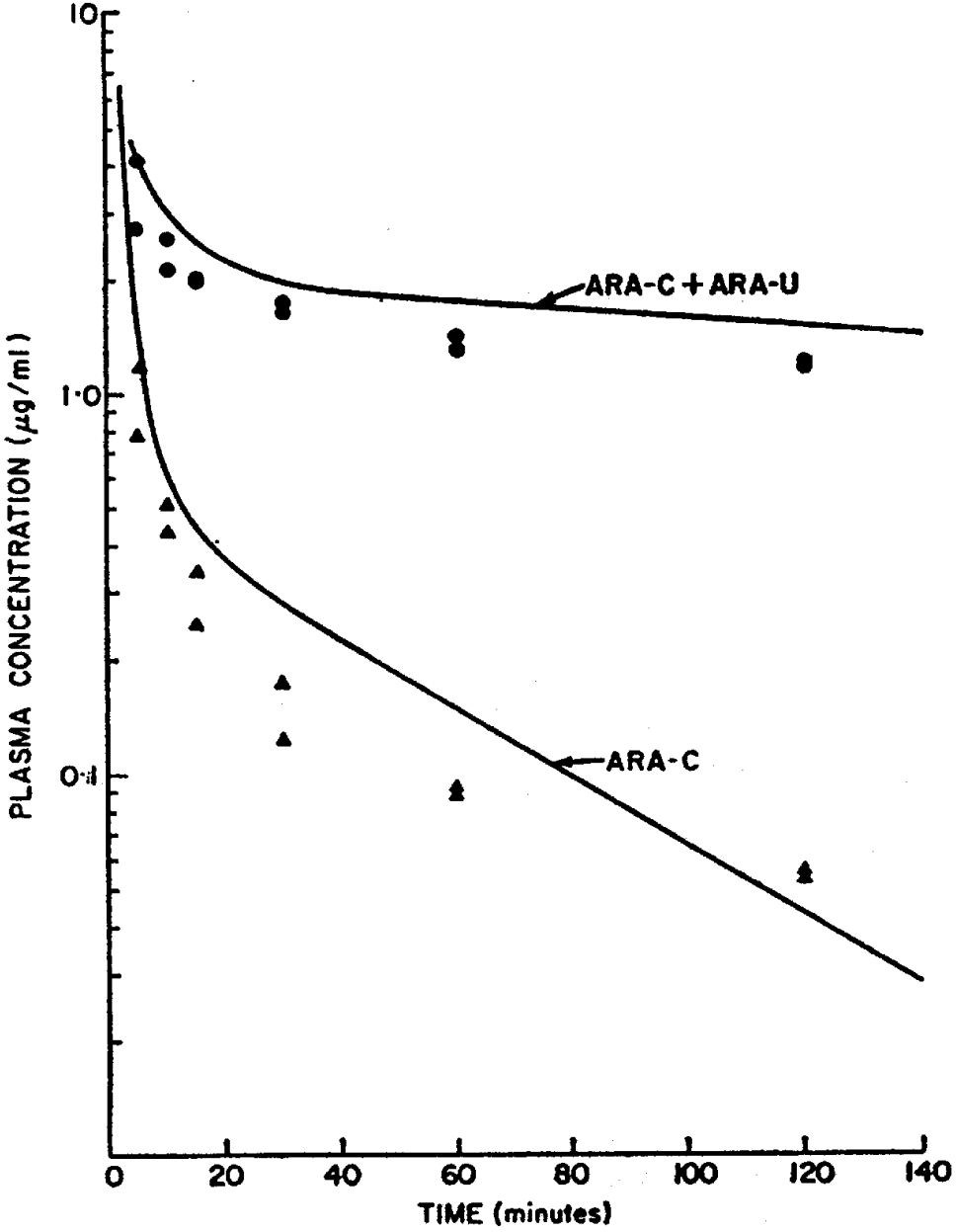
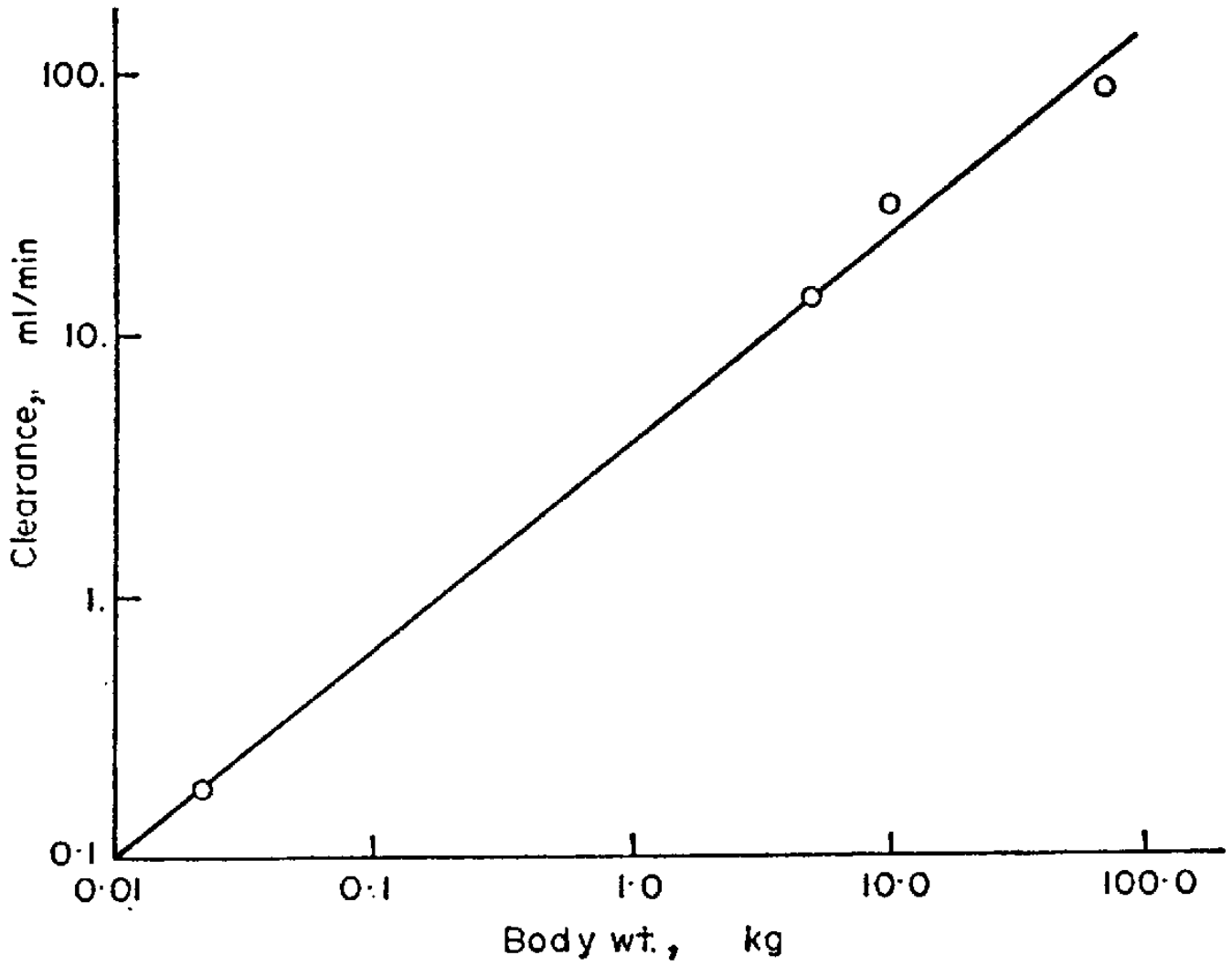
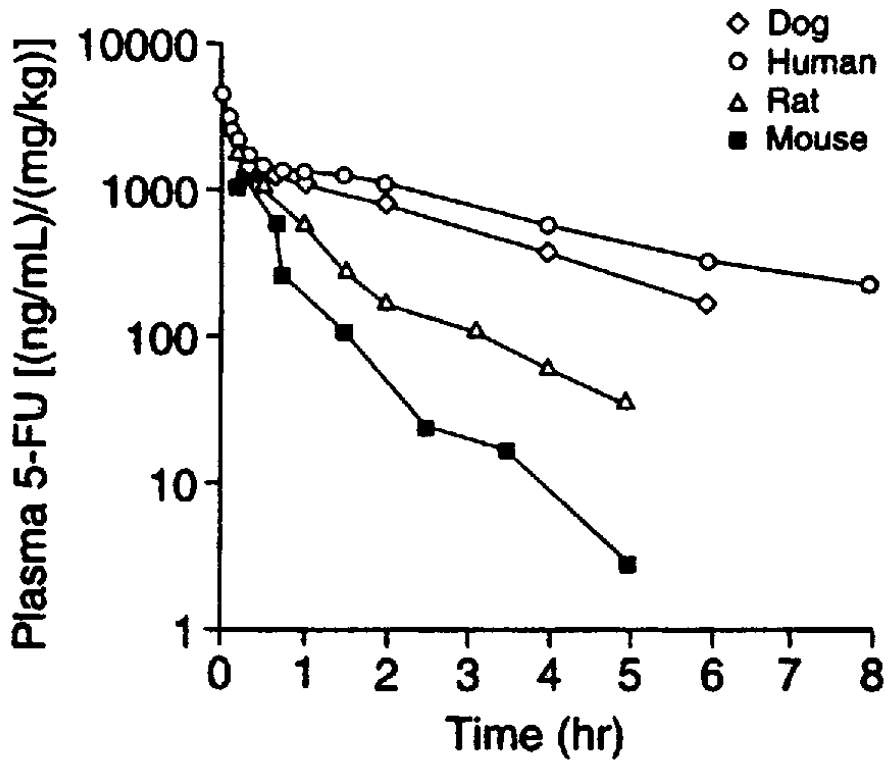


Dedrick RL et al, Biochem Pharmacol 21:1-16, 1972



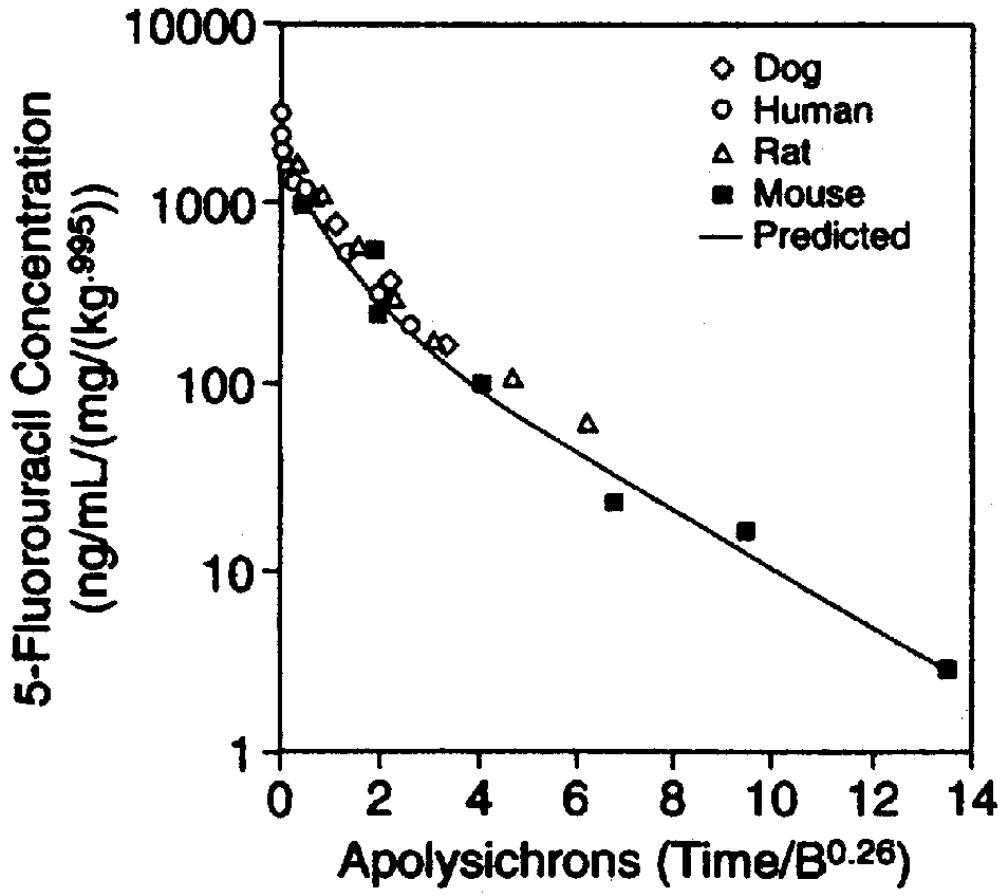
Kidney clearance of Ara-C and Ara-U vs body weight for mice, monkeys, dogs and humans

Dedrick RL et al, Biochem Pharmacol 22:2405-2417, 1973



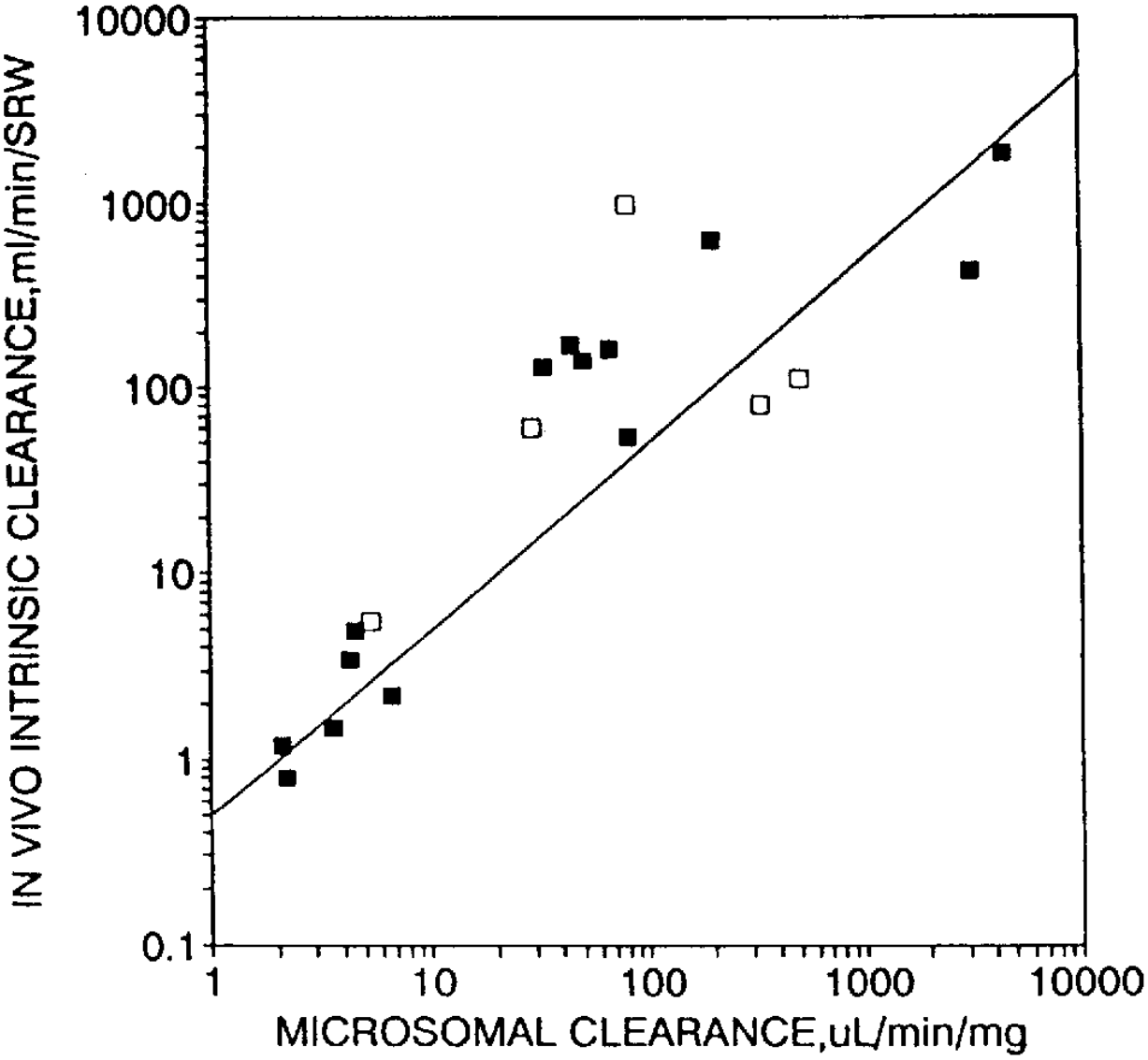
Dose-normalized plasma 5-FU concentrations in humans and animals lacking dihydropyrimidine dehydrogenase activity. The human data were obtained from a patient who was genetically deficient in DPD. The animals were treated with 776C85 to induce the DPD-deficient state

Khor SP et al. Cancer Chemother Pharmacol 39:233-238, 1997

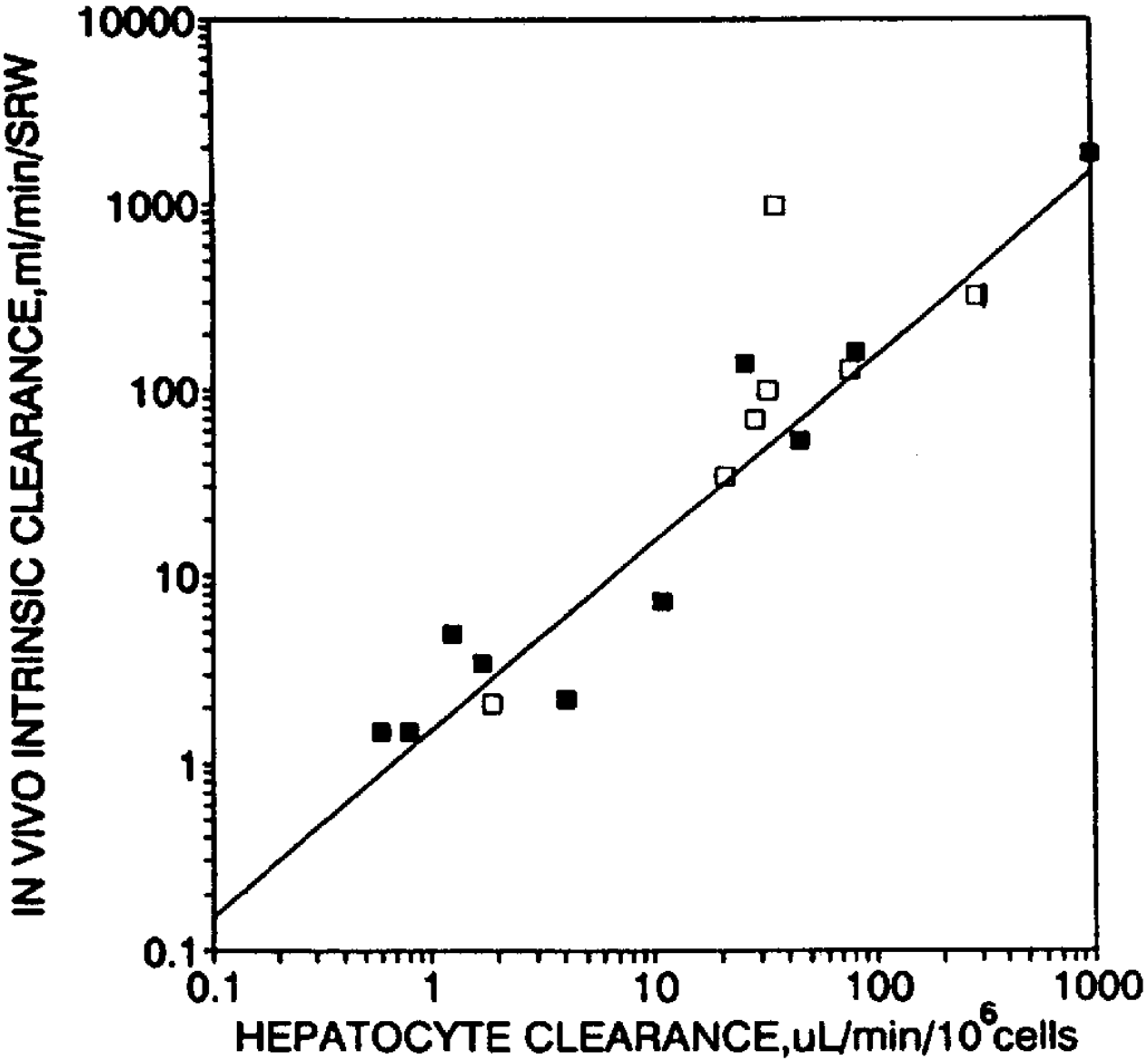


Complex Dedrick plot of 5-FU in humans and different animal species with DPD deficiency. The human data were obtained from a patient who was gentically deficient in DPD. The animals were treated with 776C85 to induce the DPD-deficient state

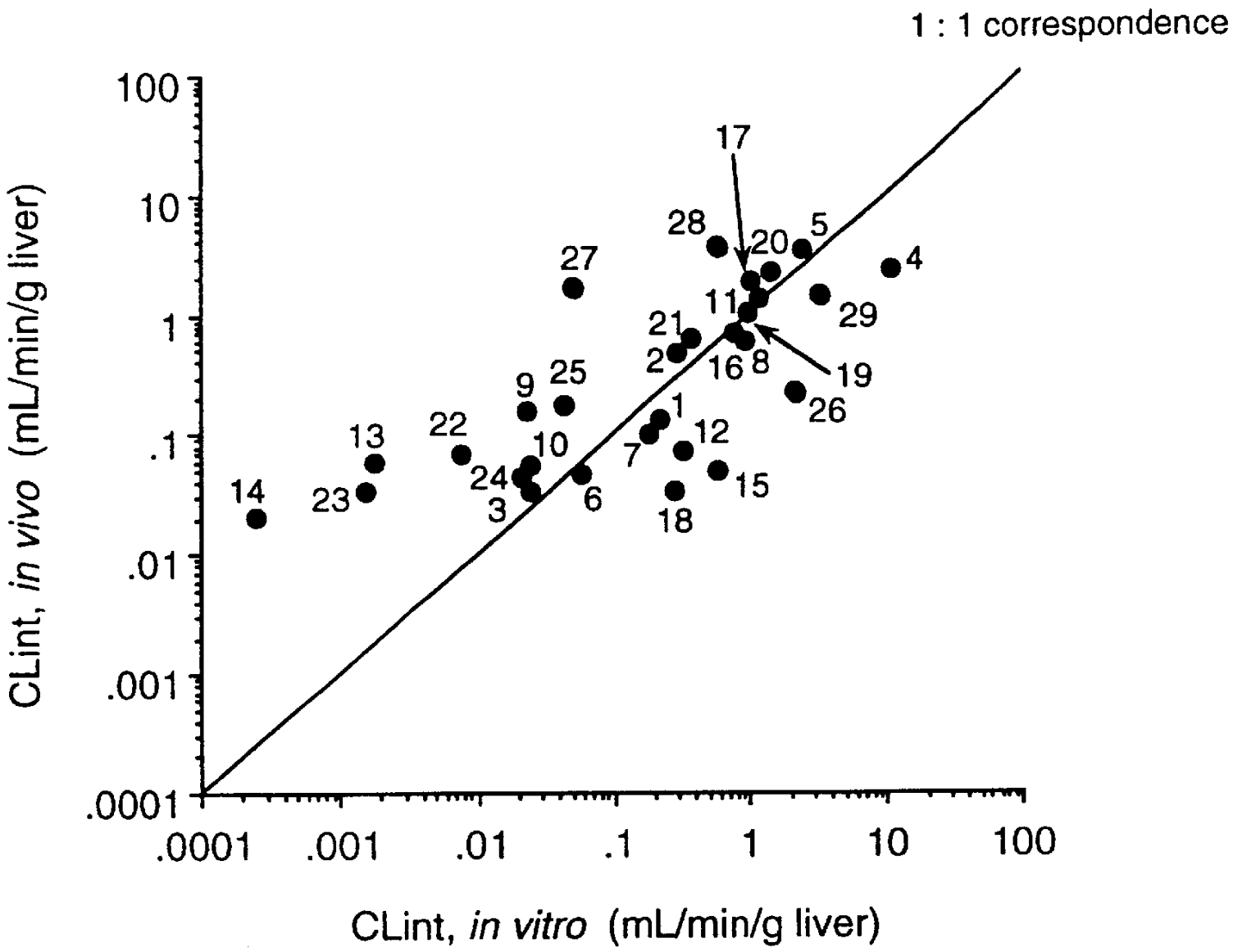
Khor SP et al. Cancer Chemother Pharmacol 39:233-238, 1997



Houston JB, Biochem Pharmacol 47:1469-1479, 1994

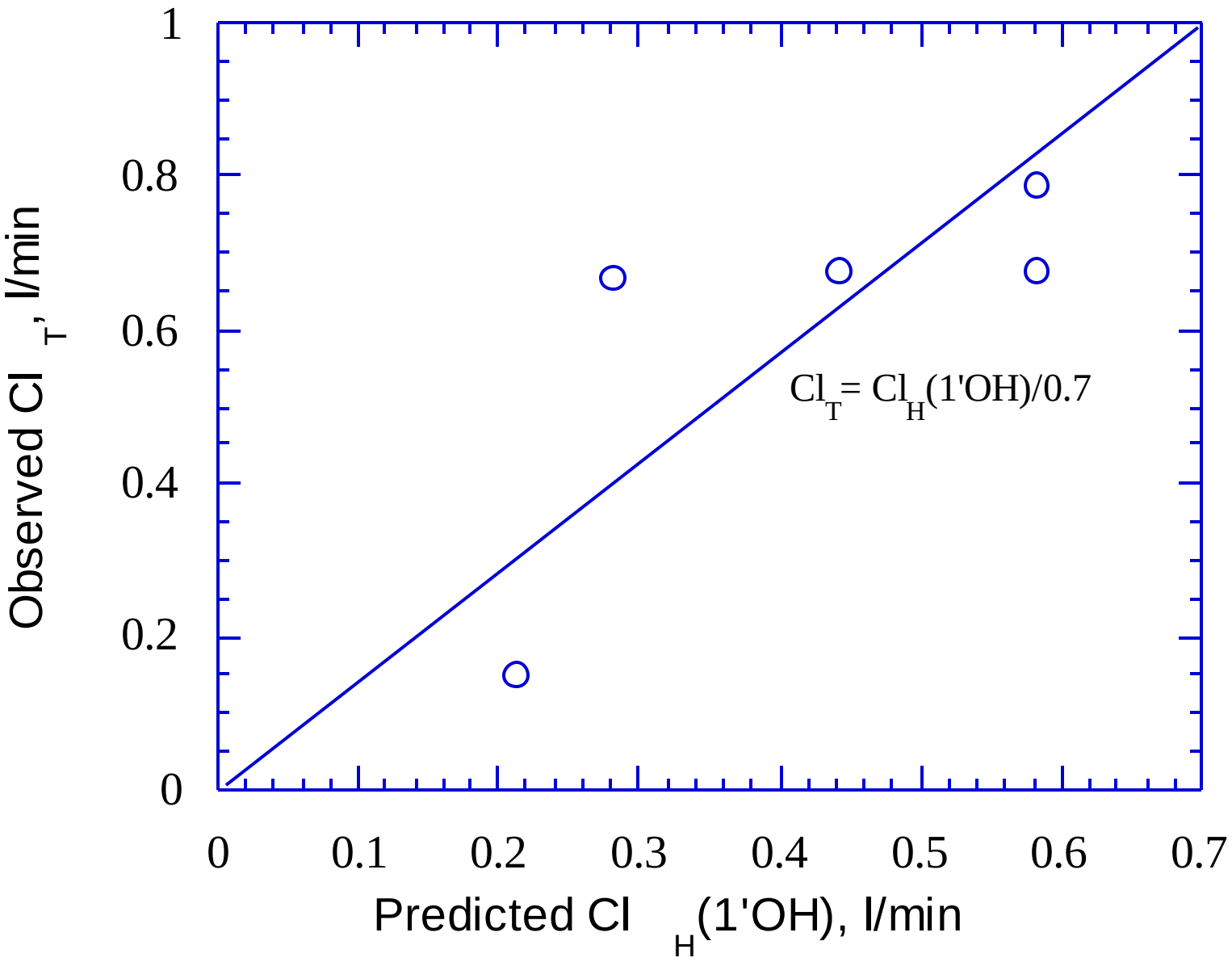


Houston JB, Biochem Pharmacol 47:1469-1479, 1994



Ito et al, Ann Rev Pharmacol Toxicol 38:461-499, 1998

Midazolam Clearance

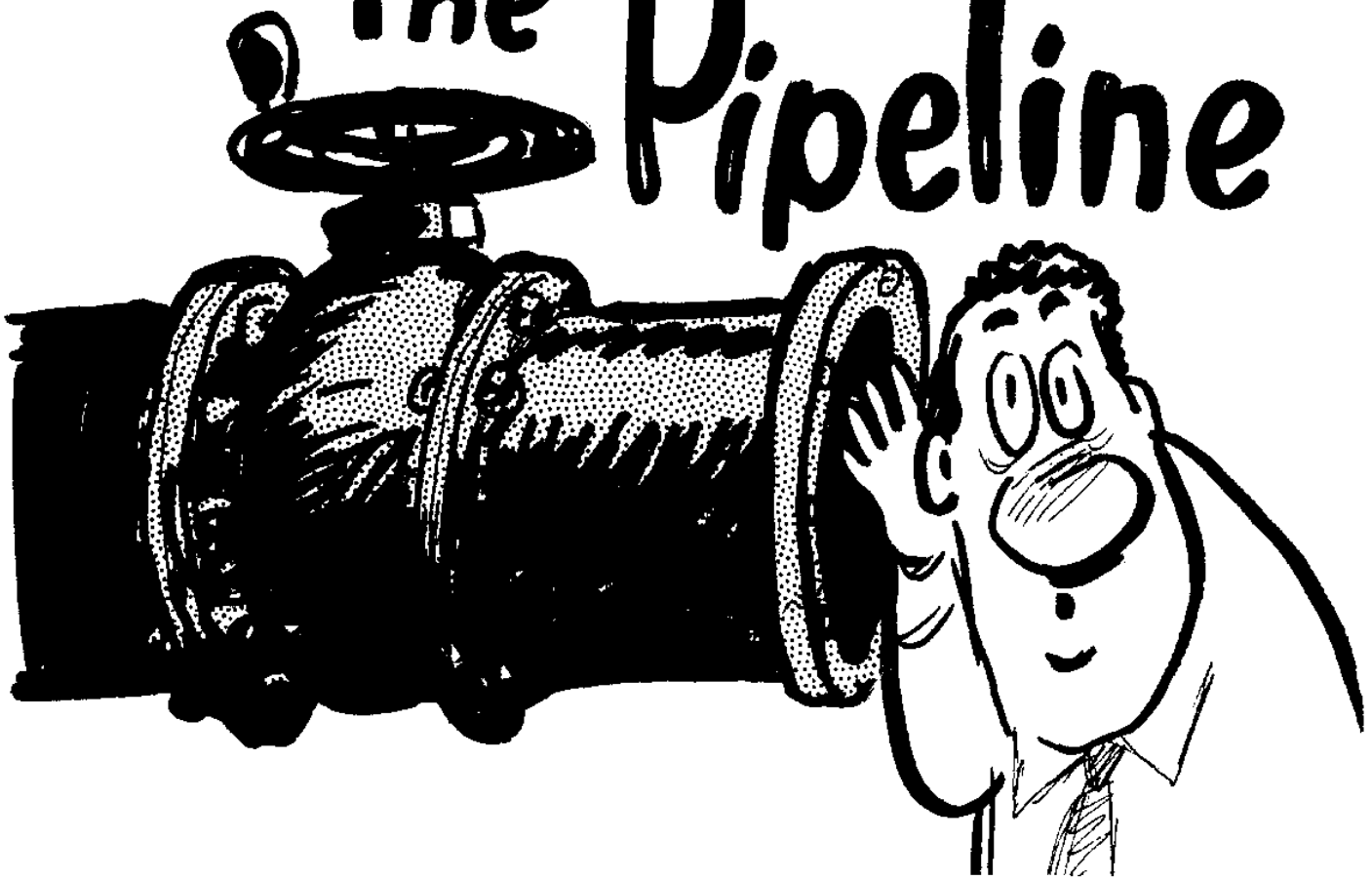


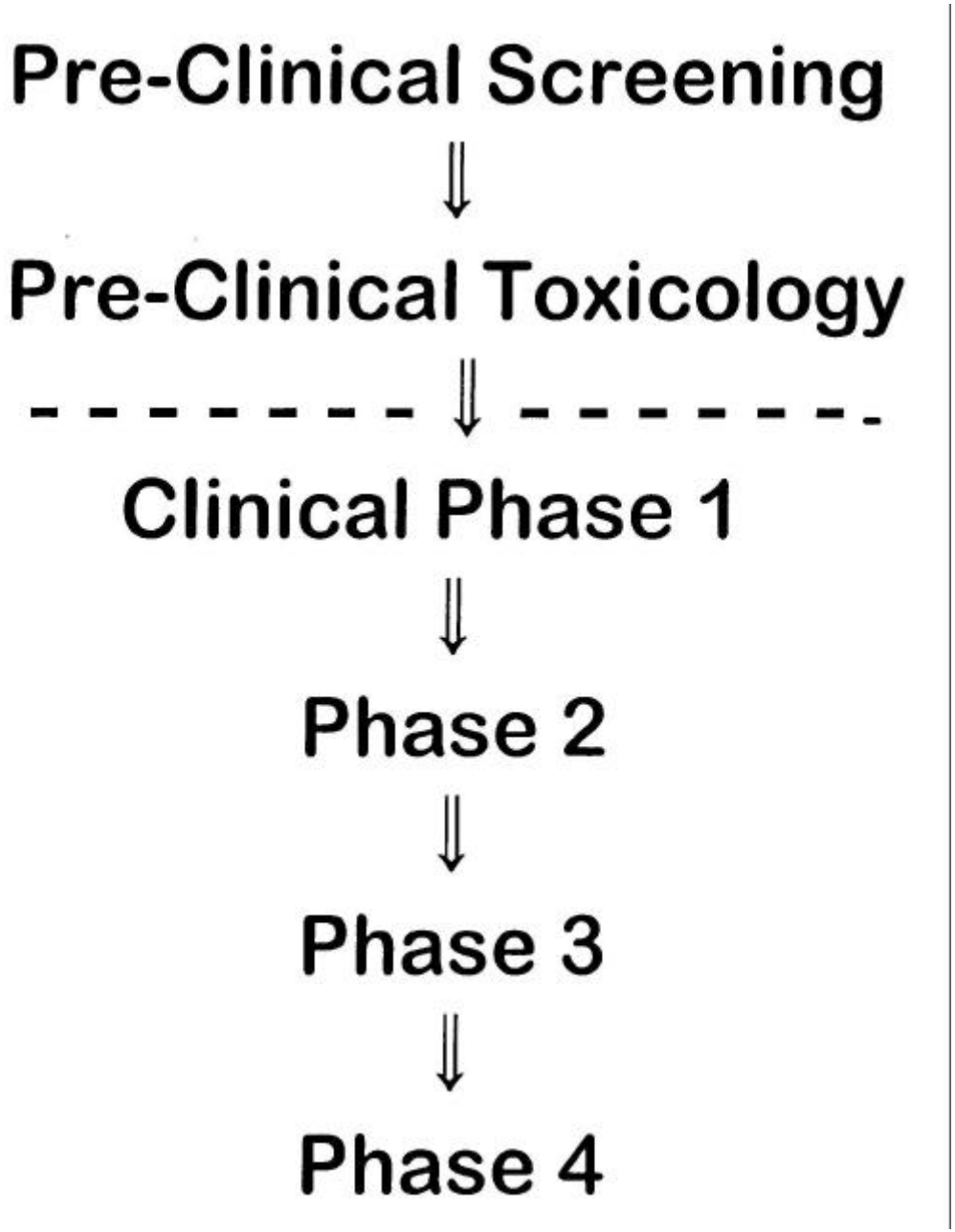
Data from Thummel et al, J PET 271:549-556, 1994.

Pharmacologically-Guided Dose-Escalation in Phase 1 (P-G-D-E)

Jerry M. Collins, Ph.D.
Lab of Clinical Pharmacology, FDA
Guest Researcher, Medicine Br, NCI

The Pipeline




Pre-Clinical Screening
Pre-Clinical Toxicology
Clinical Phase 1
Phase 2
Phase 3
Phase 4

Re-Engineering Phase I Trials

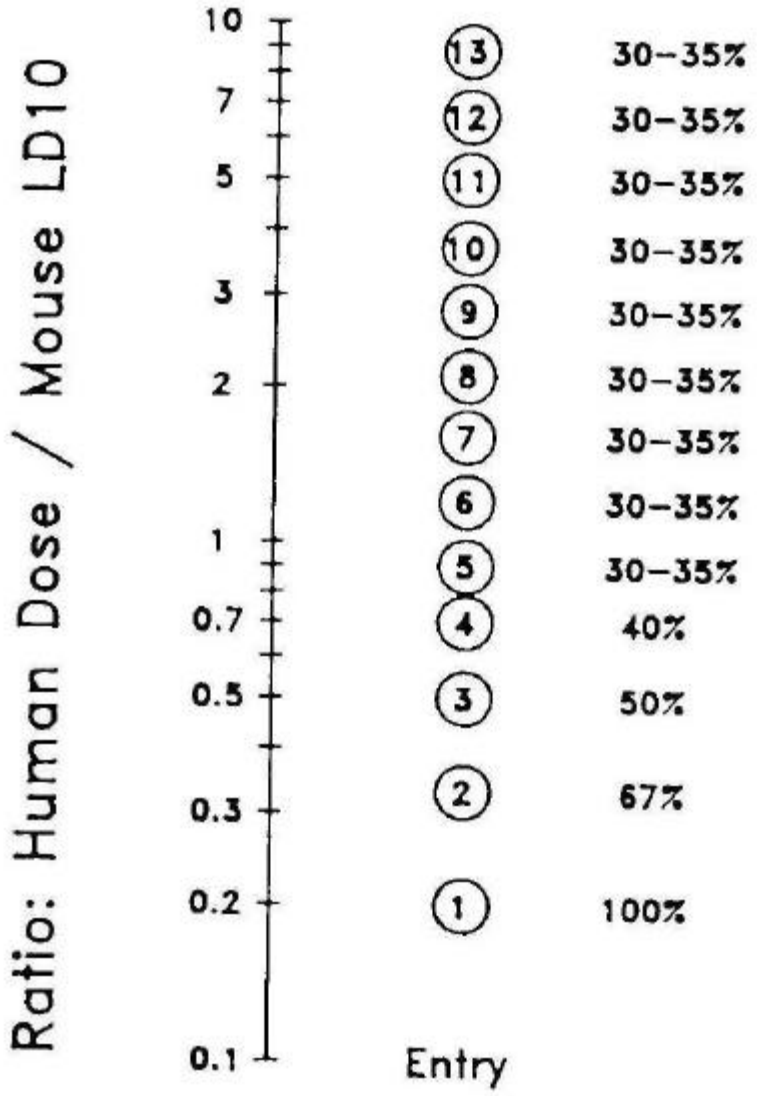
1. **Pipeline/Funnel Pressure: combinatorial/HTS, new Sponsors**
2. **To Phase I Faster, Less Preclinical Work**
3. **Fewer patients, homeopathic doses**
4. **More patients “near-Phase 2" doses**
5. **“Value-Added” factors**
   - **PK only: variability, metabolism/pharmacogenetics**
   - **PD: Decisions to Drop/Continue**

Design of Phase 1 Trial

- **Starting Dose**
- **Escalation Scheme**

For Both Elements, Conflict Between Caution/Safety vs. Efficiency/Efficacy

Modified Fibonacci Escalation



BIBLIOGRAPHY / COLLINS / PHASE 1

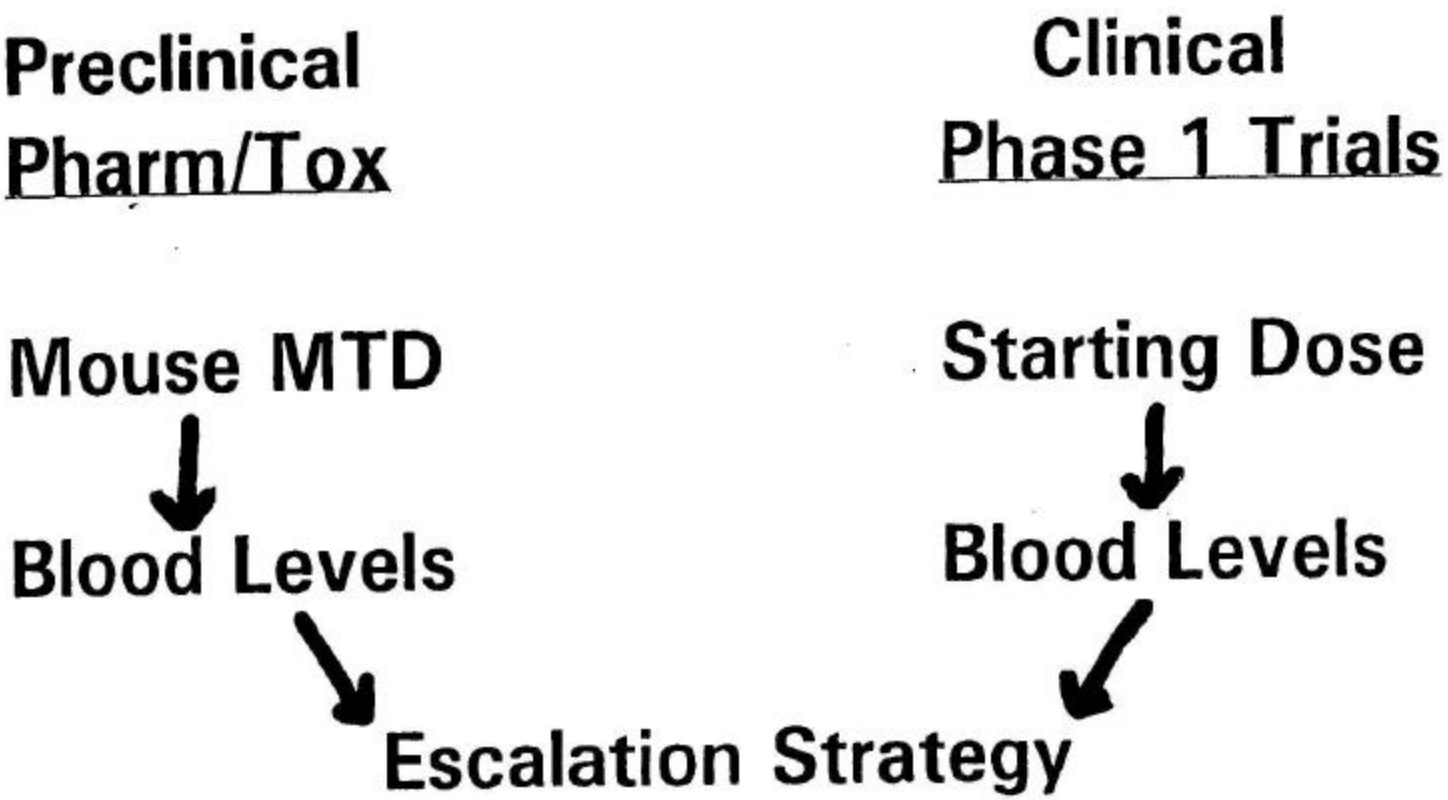
J.M.Collins, D.S. Zaharko, R.L.Dedrick, B.A.Chabner.
Potential roles for preclinical pharmacology in Phase I trials.
Cancer Treat. Rep. 70:73 - 80, 1986.
***** Message: we do a lot of preclinical pharm studies;***
- - what do we learn?
- - how is it used?
***** Initial proposal for customized dose escalation.***

J.M. Collins, C.K. Grieshaber, B.A. Chabner.
Pharmacologically-guided Phase I trials based upon preclinical development.
J. Natl. Cancer Inst. 82:1321-1326, 1990.
***** Note that title doesn't say "PK"***
Intended as an overall platform
Summarizes mostly retrospectively

PK-PD Hypothesis:

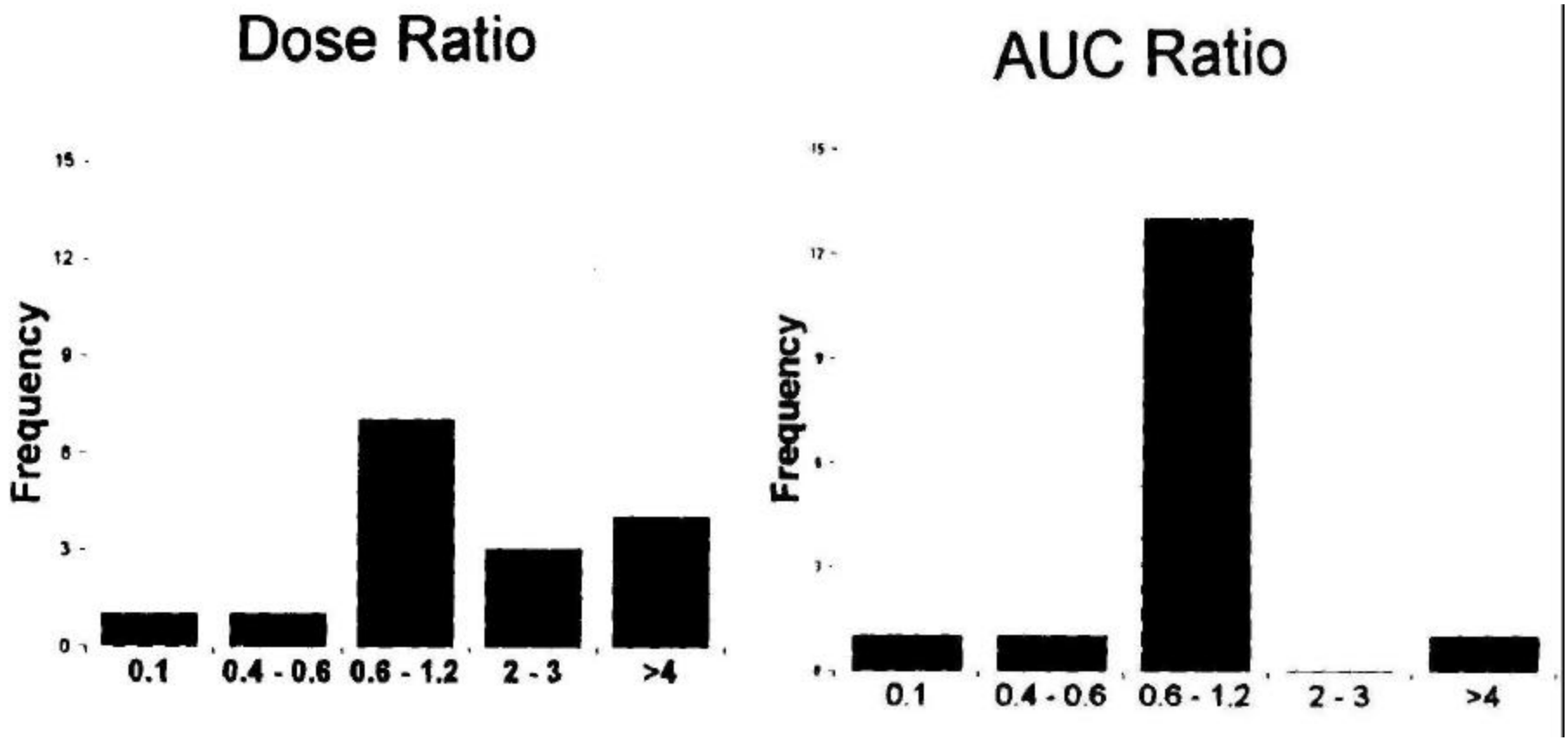
When Comparing Animal and Human Doses, Expect Equal Toxicity for Equal Drug Exposure

Bridges Between Preclinical and Clinical Development



Acute Toxicity of Anticancer Drugs:

Human versus Mouse



Conclusion:

Hypothesis has merit.

Follow-Up:

What is underlying reason for interspecies differences?

S.Markey, 3-Dec-98

Additional Effects on Drug Metabolism

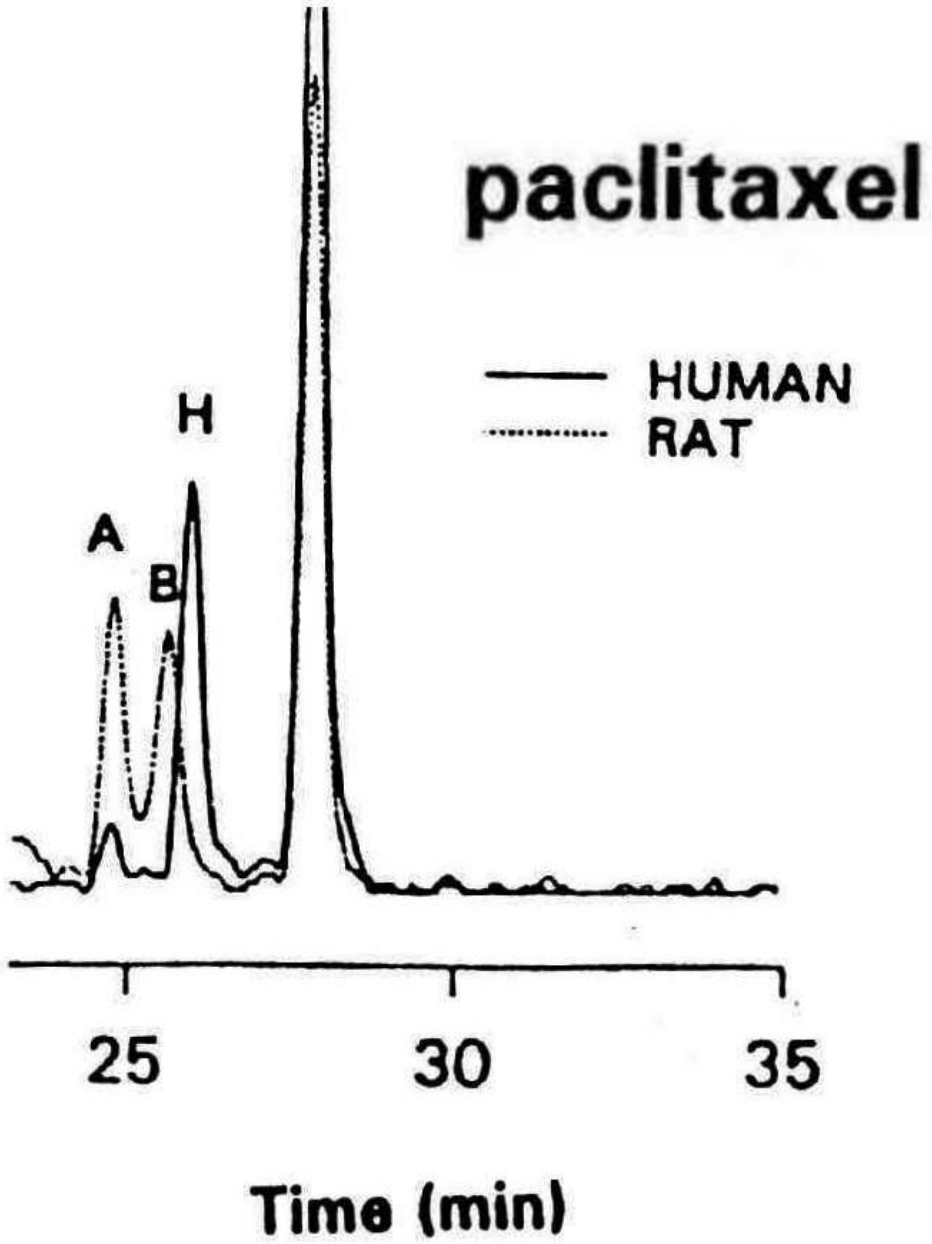
Species differences

- Major differences in drug metabolism in different species have been recognized for many years (R.T. Williams) both in gut microflora and CYP proteins.
- Example: phenylbutazone half-life is 3 h in rabbit,6 h in rat, guinea pig, dog and 3 days in humans.
- Example: hexobarbital sleeping time and half-life are directly correlated in various species.
- Species strain differences are pronounced, not only for oxidations, but also for conjugations.

Gianni et al, JNCI (1990)

AUC values in plasma for Iododeoxydoxorubicin (I-Dox) in Mouse & Humans at Equi-Toxic Doses

	Mouse	Human
I-Dox	5.0	0.3
I-Dox-ol (metabolite)	1.2	4.0


paclitaxel
HUMAN
RAT
H
A
B
25
30
35
Time (min)

In Addition to Explaining Interspecies Differences, Other Applications for Metabolism Studies in Phase 1:

Learn/Confirm Major Pathways
Learn/Confirm Active/Toxic Molecules

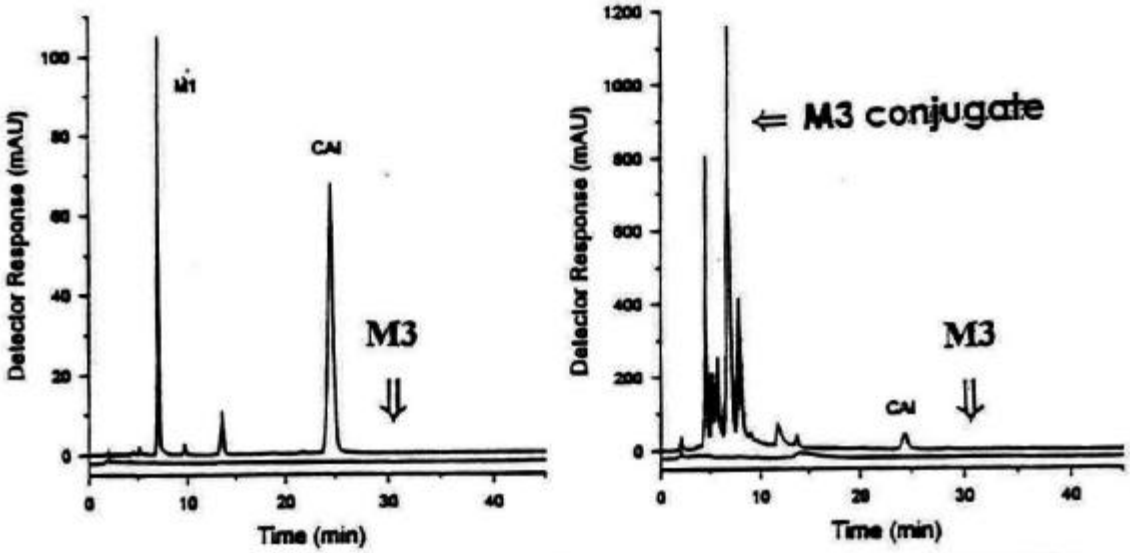
In Vitro - In Vivo Metabolic Profiling

"CAI"

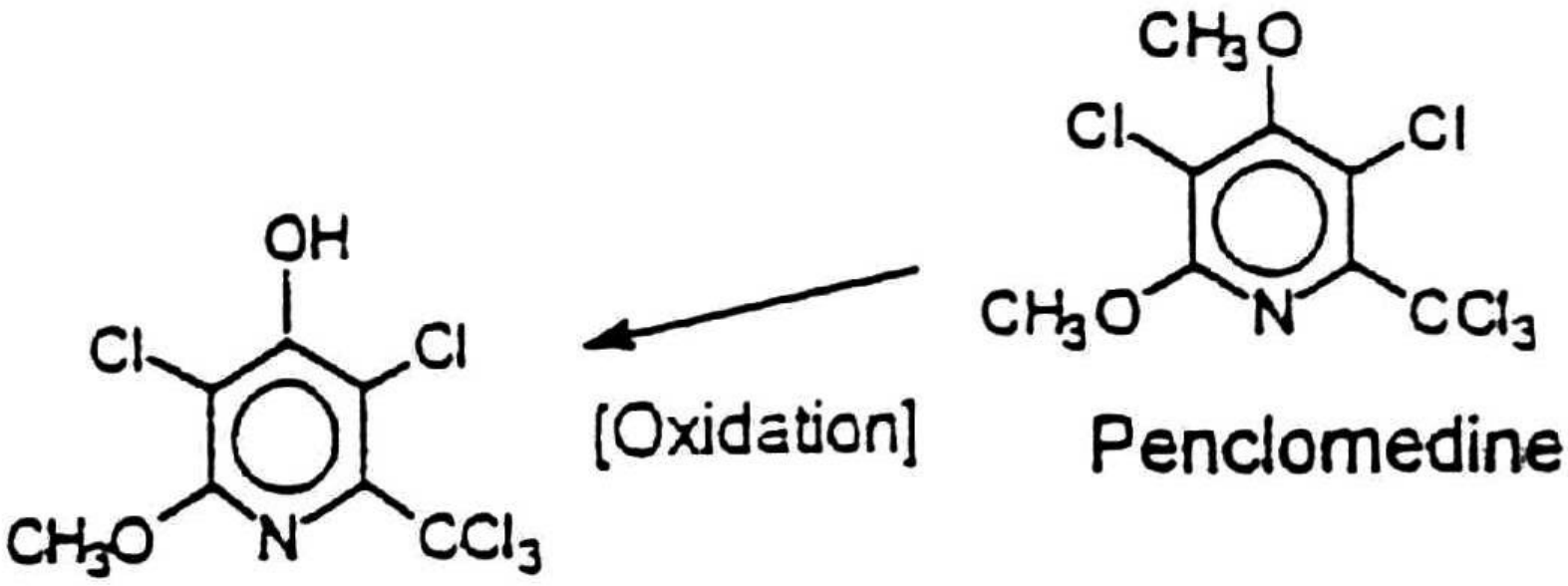
Microsomes

M1 2%

M3 84%



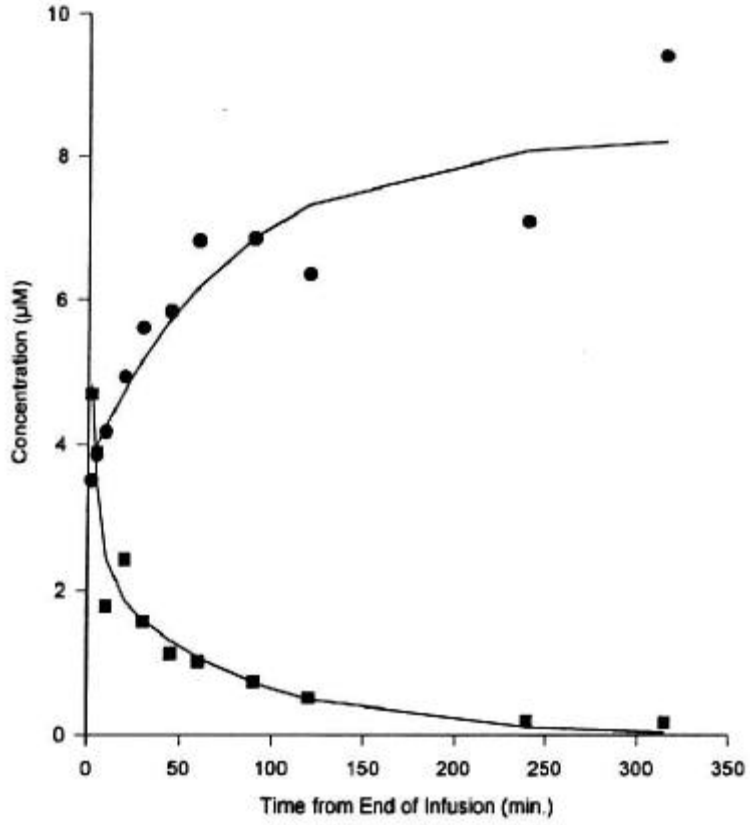
L. Ludden et al Clin Cancer Res, 1995

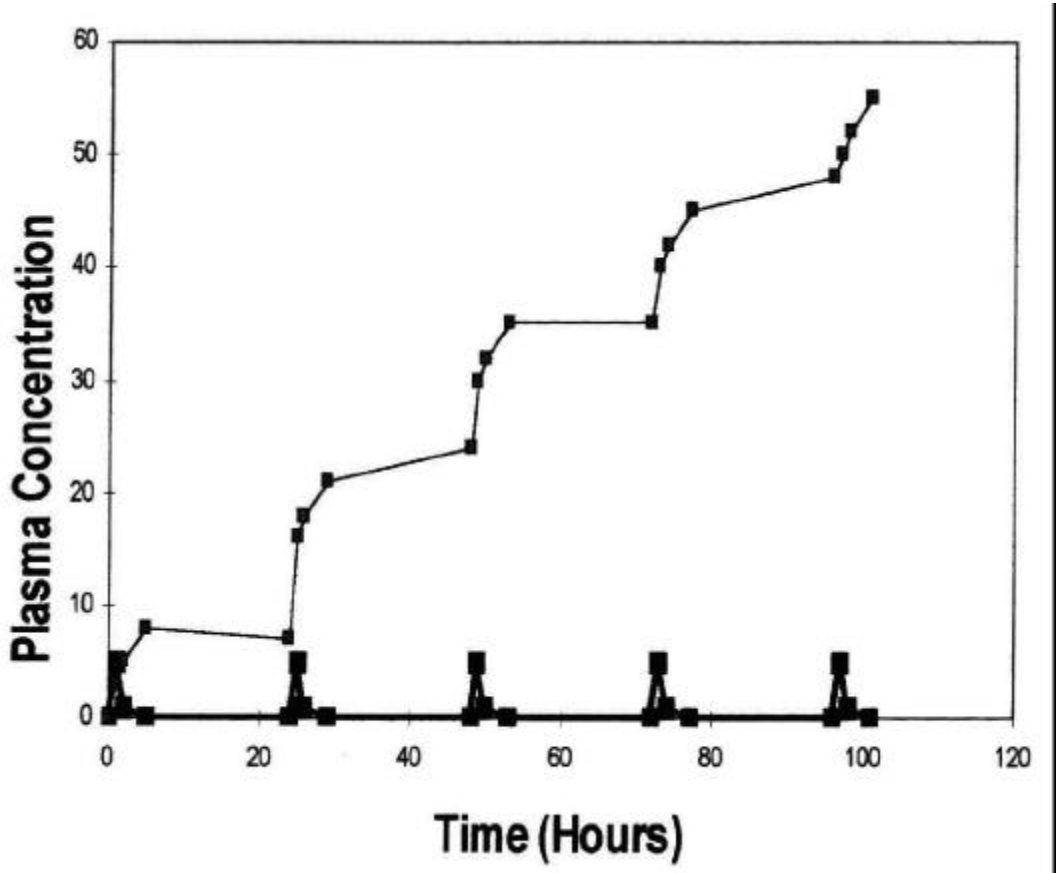


Penclomedine

Demethyl-Penclomedine

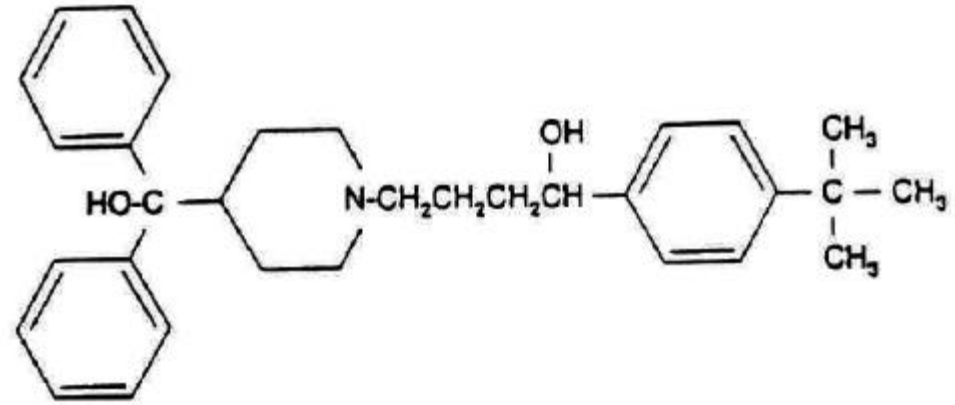
N. Hartman et al, Clin Cancer Res, 1996

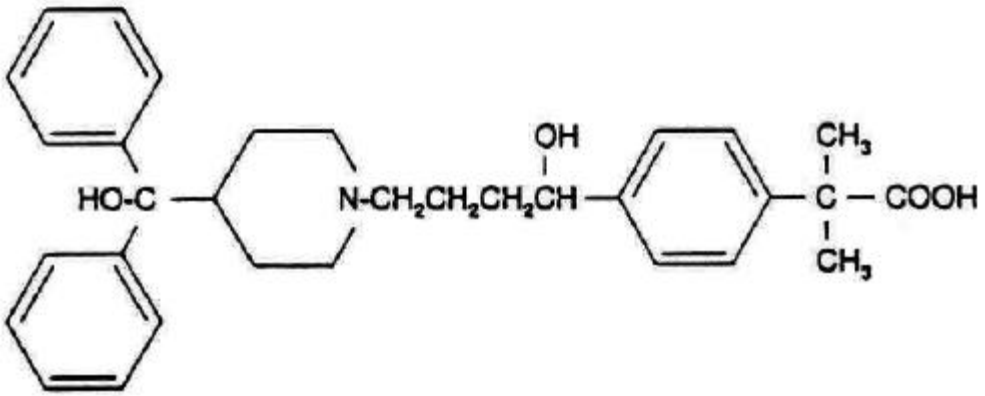




N. Hartman et al, Clin Cancer Res, 1996

terfenadine/SELDANE®





fexofenadine/ALLEGRA®

Functional Imaging via PET: Biomarkers for Treatment Evaluation

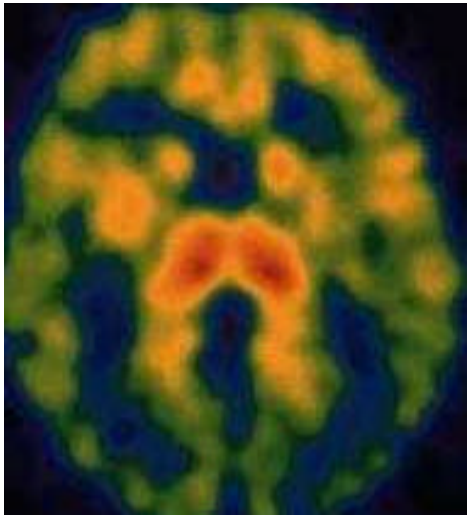
- - Does treatment impact the desired target?
- - What is the minimum/maximum dose?
- - How to select interval between courses?

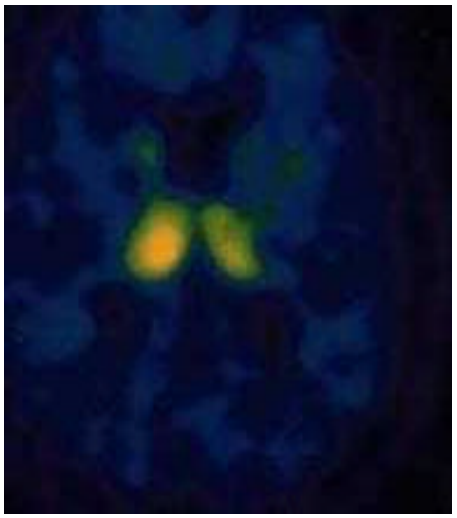
CONTEXT:
Individual Patient, or New Agent Development

Limitation: **lack of probes**

Fowler, Neurology (1993) MAO-B Inhibitor Lazabemide

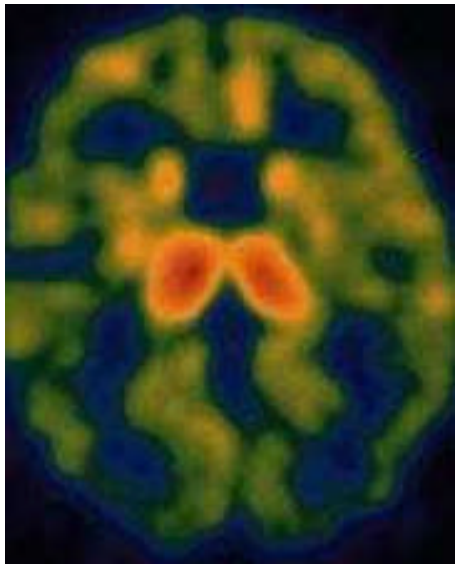
baseline





25 mg bid

50 mg bid



36 hrs later

Simon et al, JNCI, April 1997
"Accelerated Titration Designs"

Database → Model → Simulations

Re-Examine Long-Held Traditions:

*** More than 1 patient per dose level?**
*** Grade 1 toxicity: any impact on trial?**
*** First Grade 2 toxicity impact on trial?**
*** Intra-Subject Escalation?**
*** Double as long as you can?**

What is Inherent in Phase 1 Trials?

<surprise!>