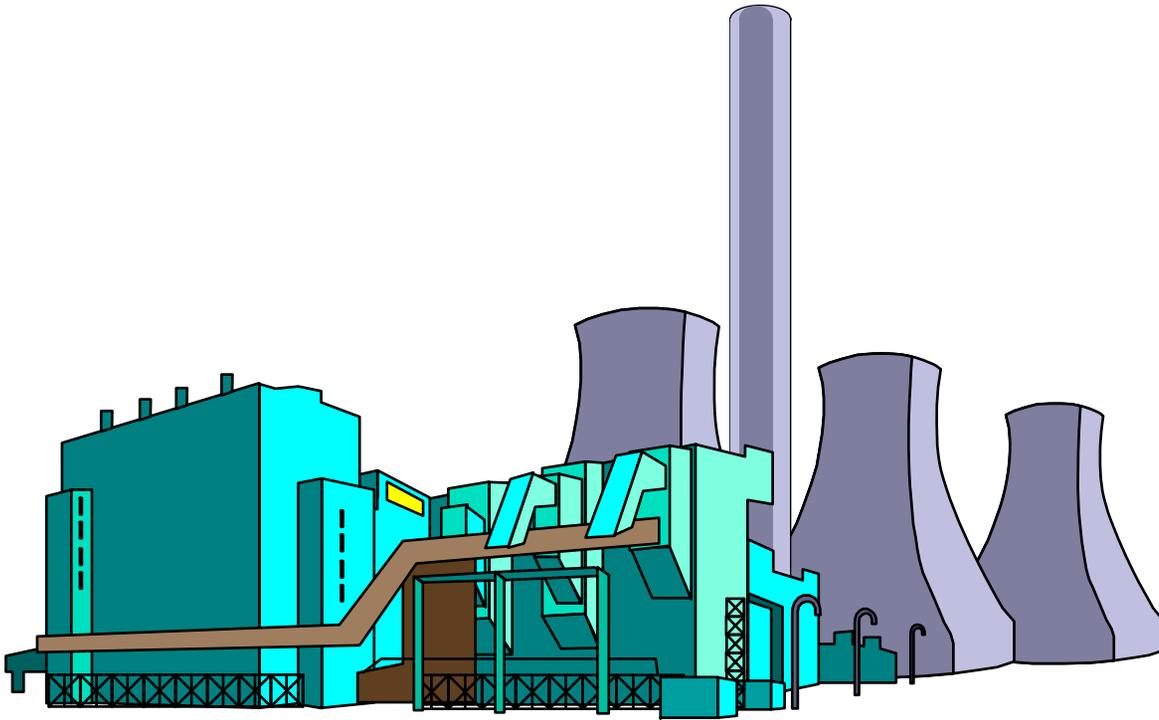


Animal Scale-Up

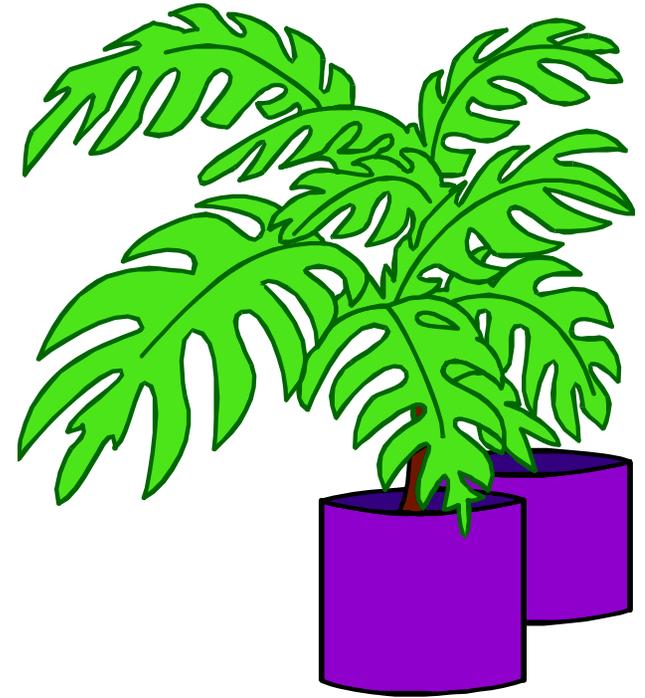
Robert L. Dedrick, Ph.D.

**Laboratory of Bioengineering and Physical Science,
National Institute of Biomedical Imaging and
Bioengineering, NIH**

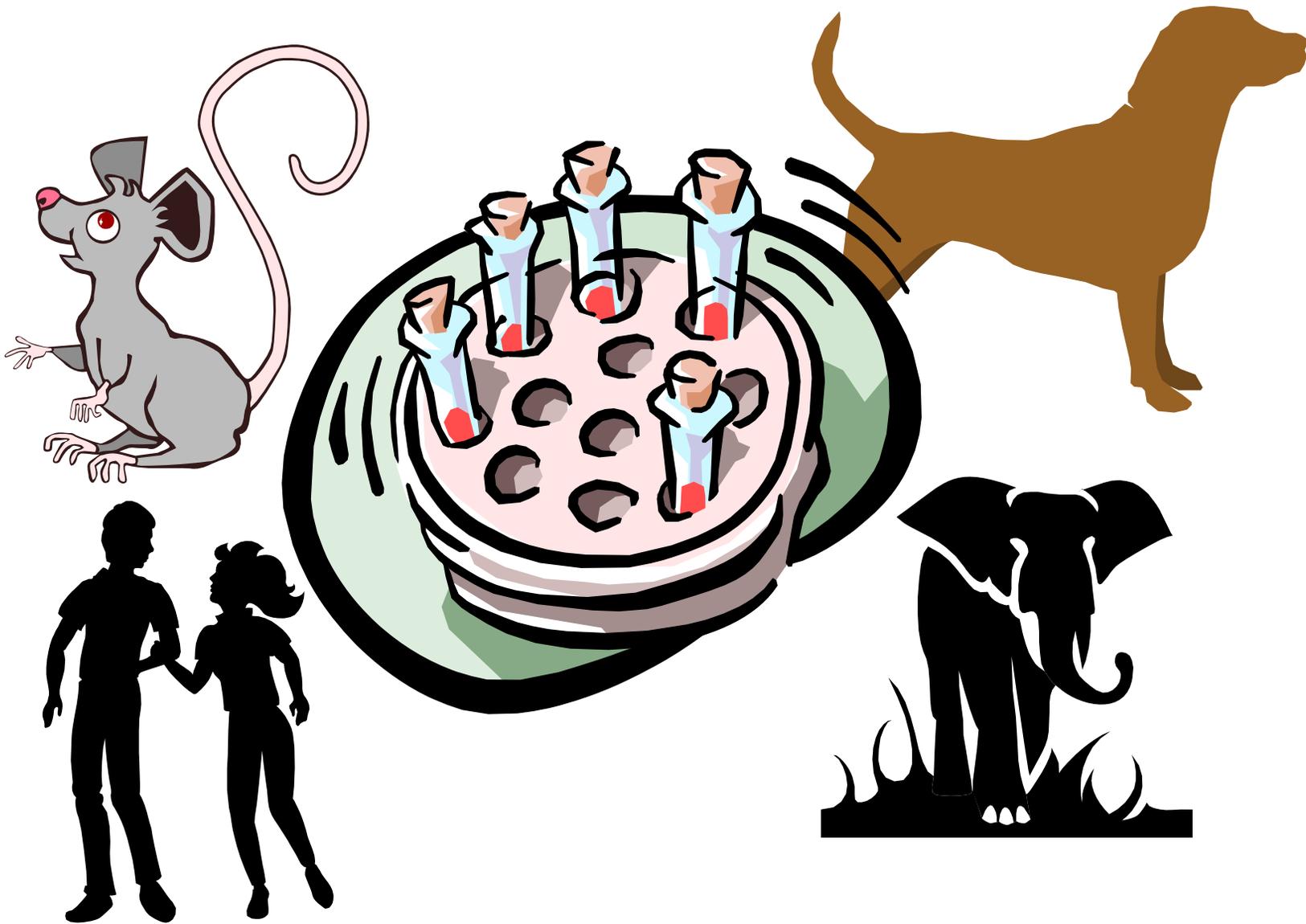
April 2, 2009



Chemical Plant



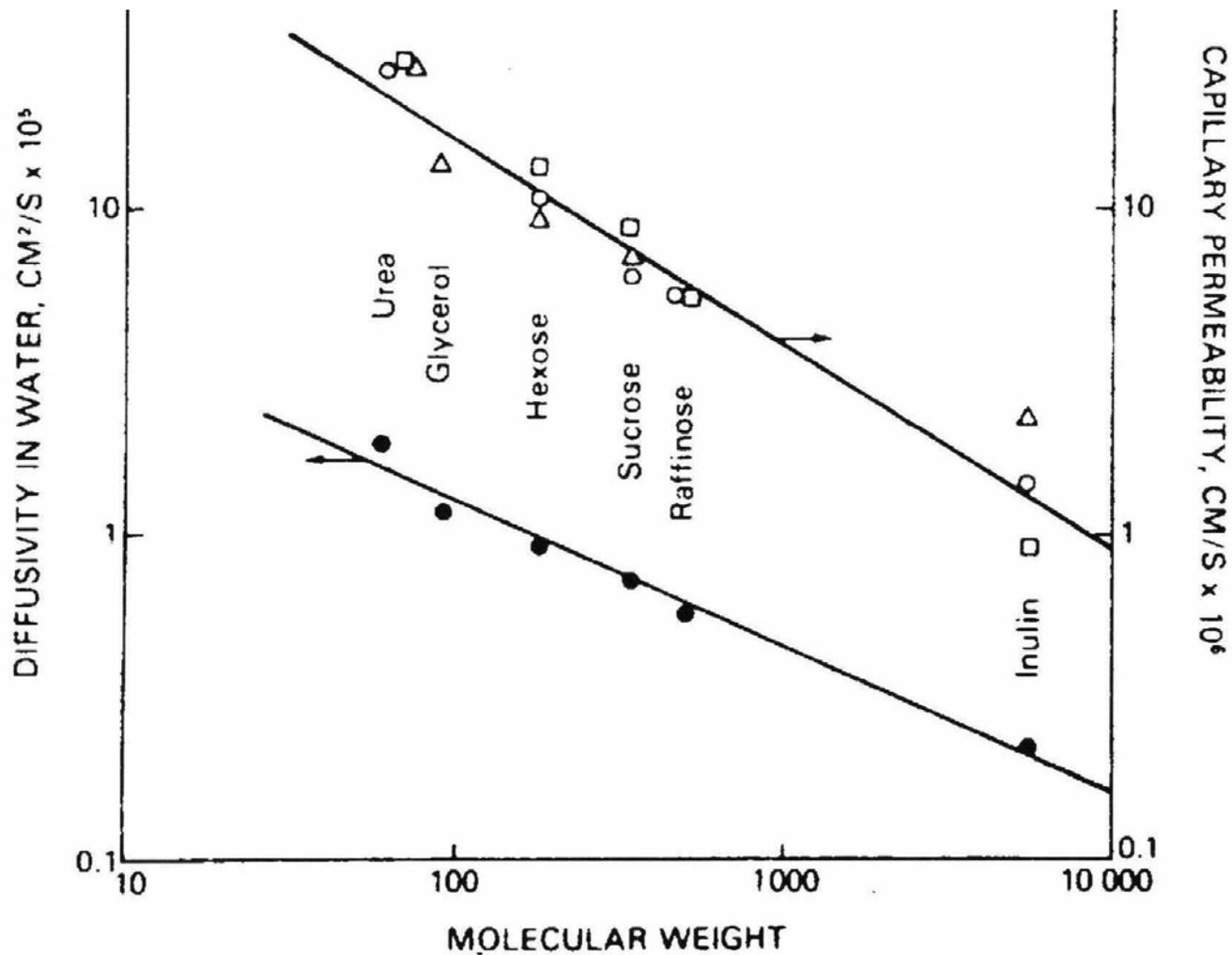
Biological Plant











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

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

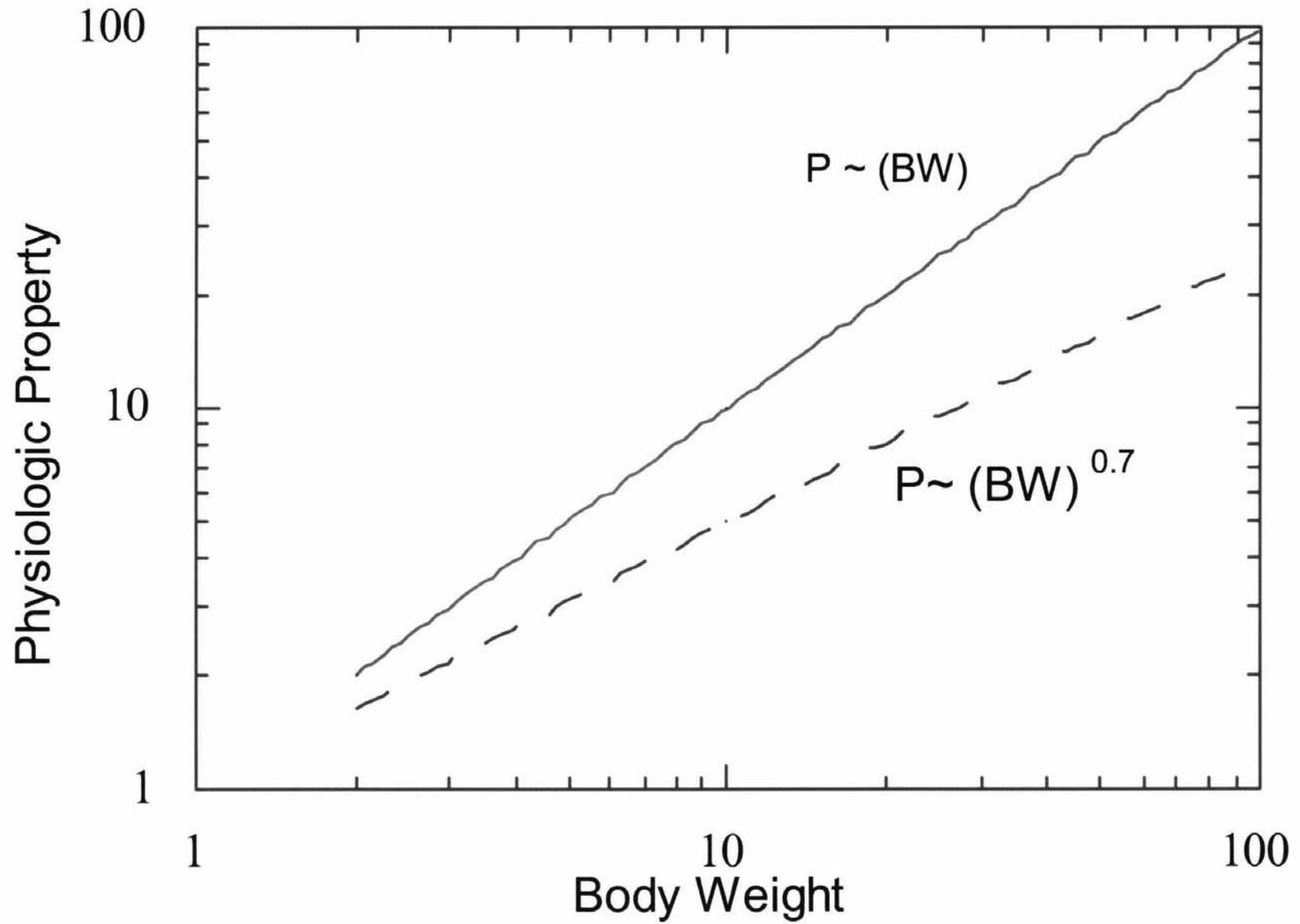
where P = physiological property or anatomic size

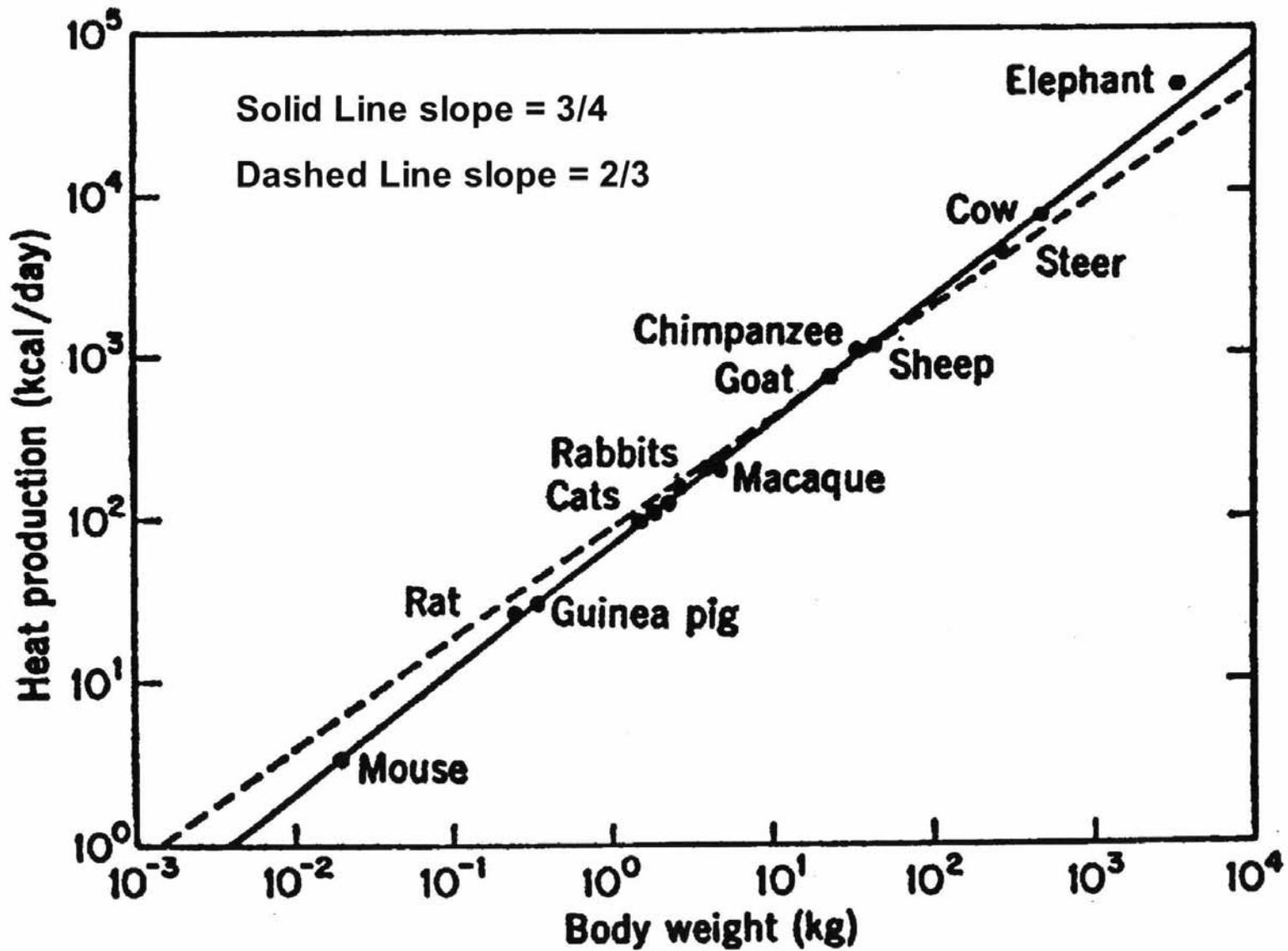
a = empirical coefficient

BW = body weight

m = allometric exponent

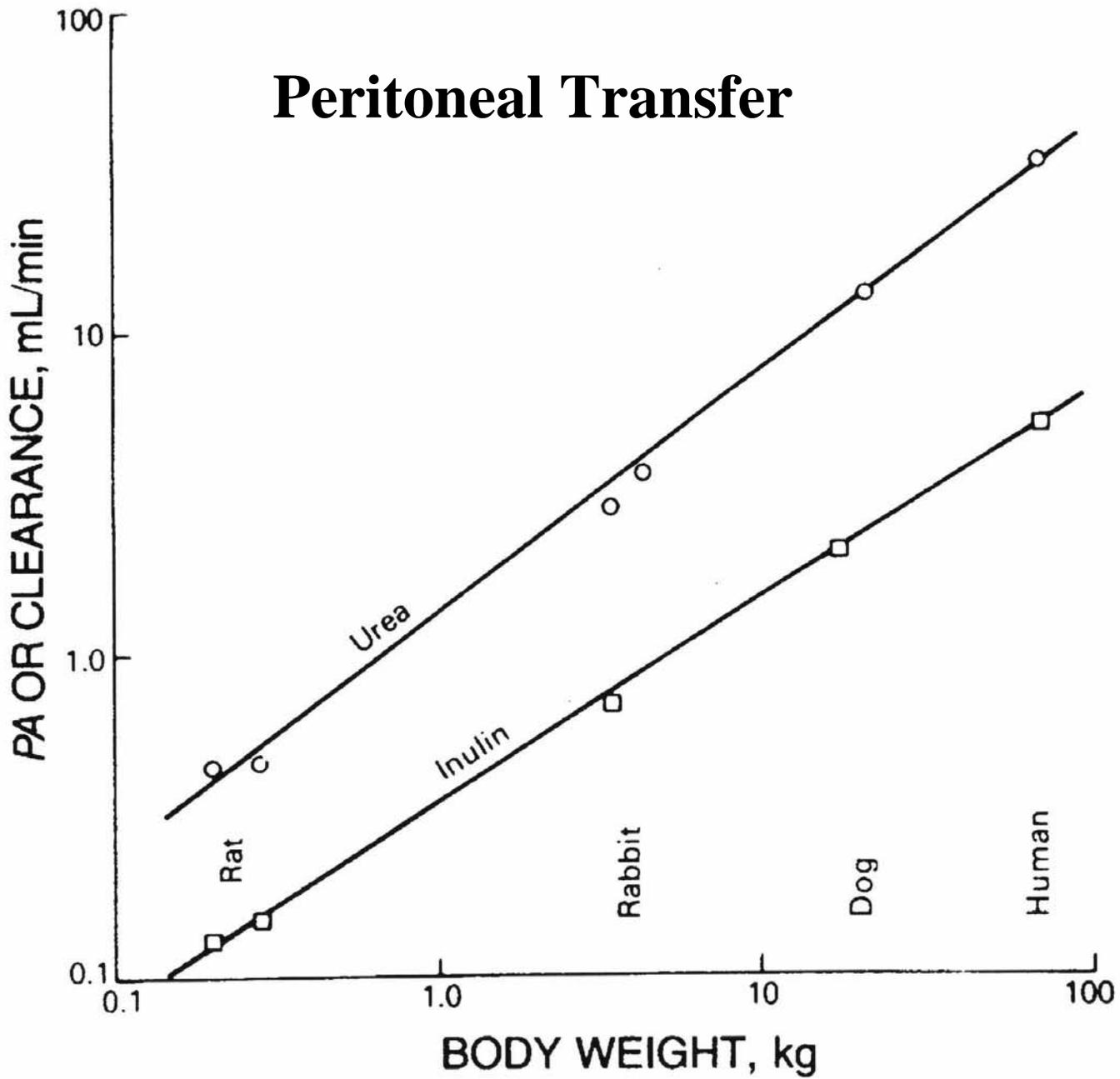
Allometric Chart



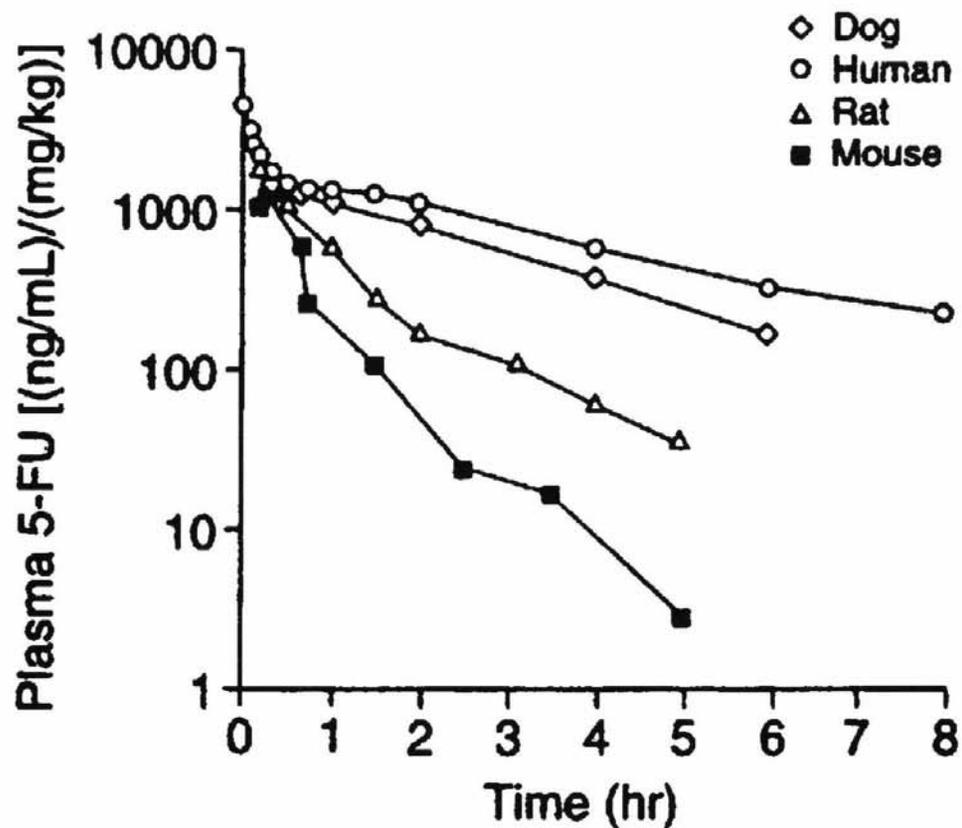


McMahon T. Science 179:1201-1204, 1973

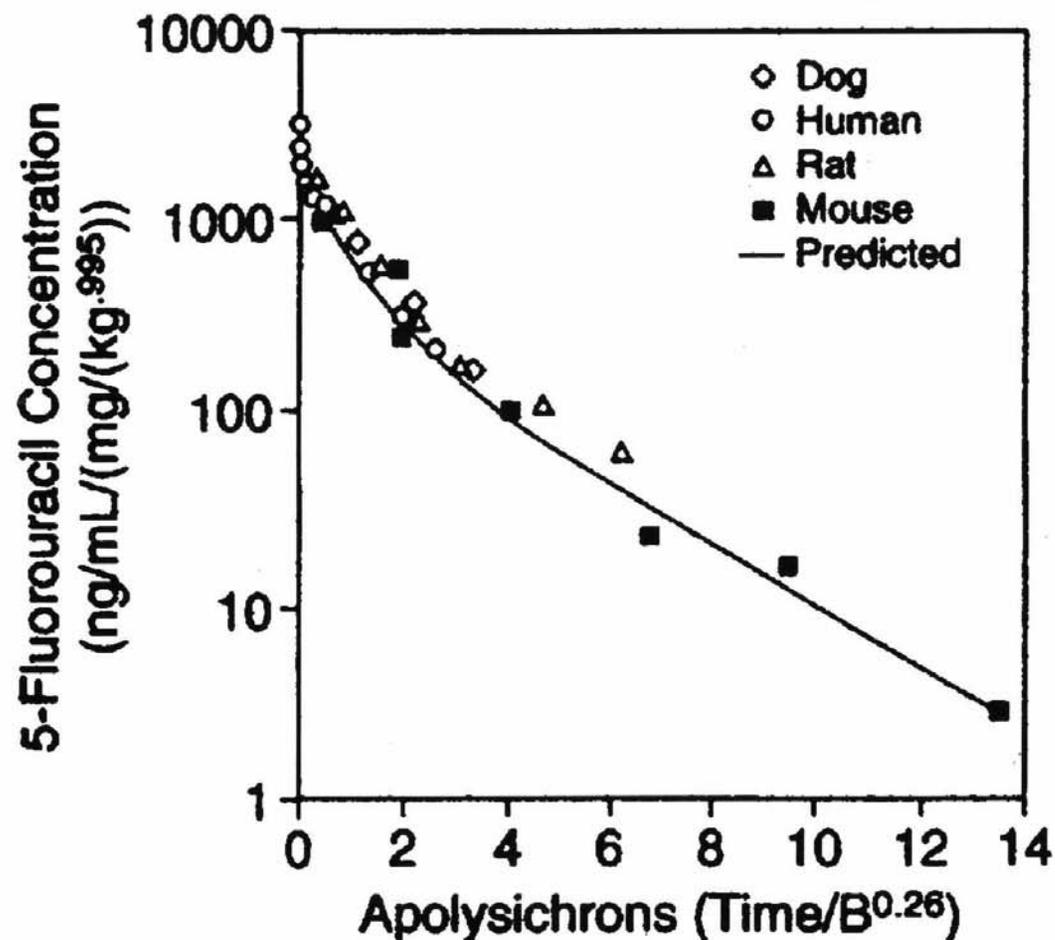
Peritoneal Transfer



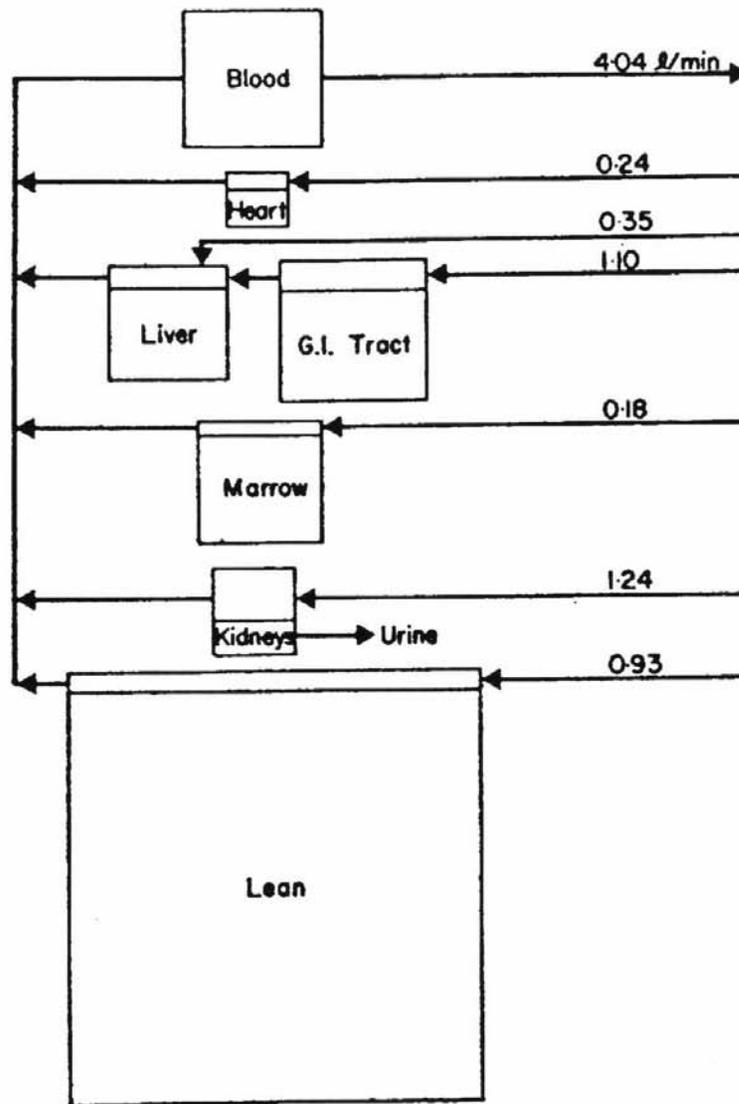
Dedrick RL et al, ASAIO J 5:1-8, 1982



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



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 genetically deficient in DPD. The animals were treated with 776C85 to induce the DPD-deficient state



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

C = drug concentration, $\mu\text{g/ml}$

t = time, min

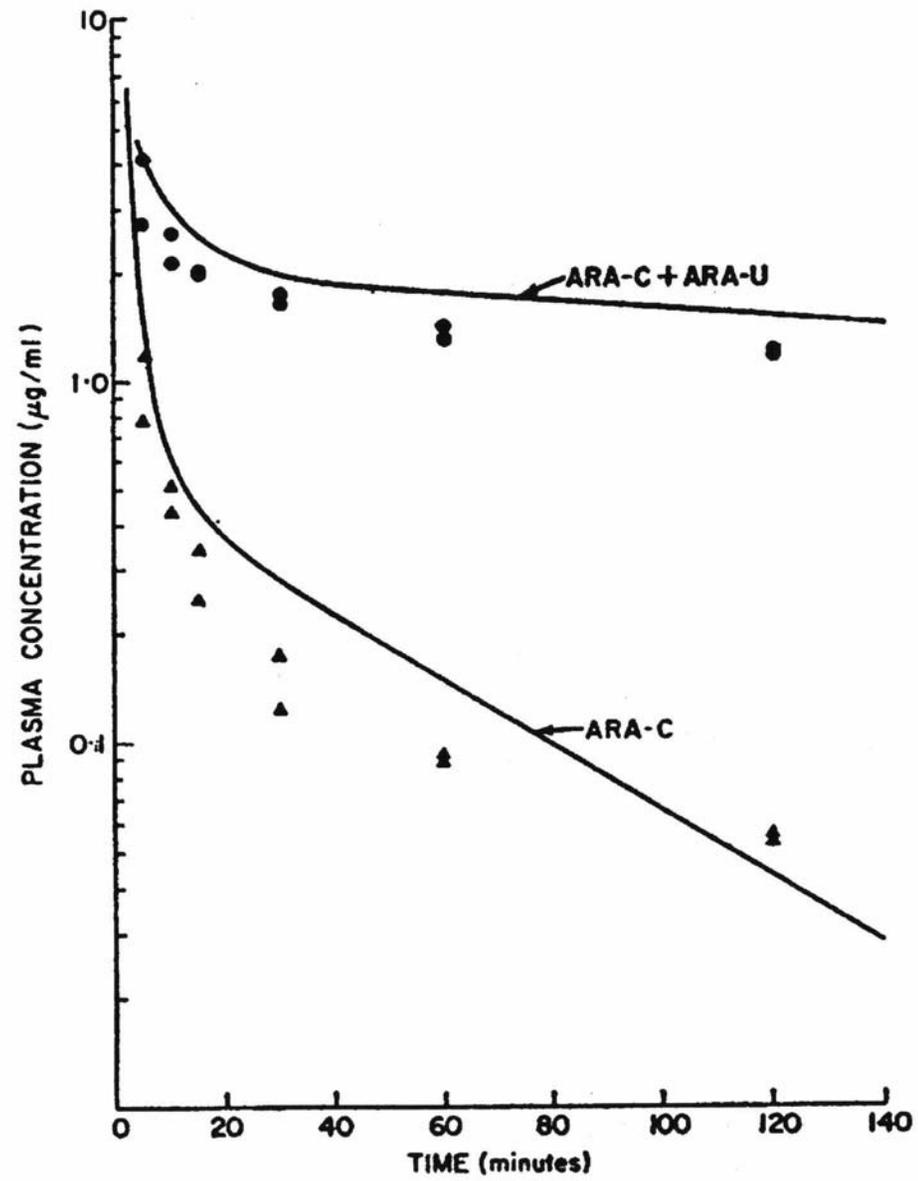
Q = blood flow rate, ml/min

v_{\max} = maximum rate of metabolism, $\mu\text{g/min ml}$

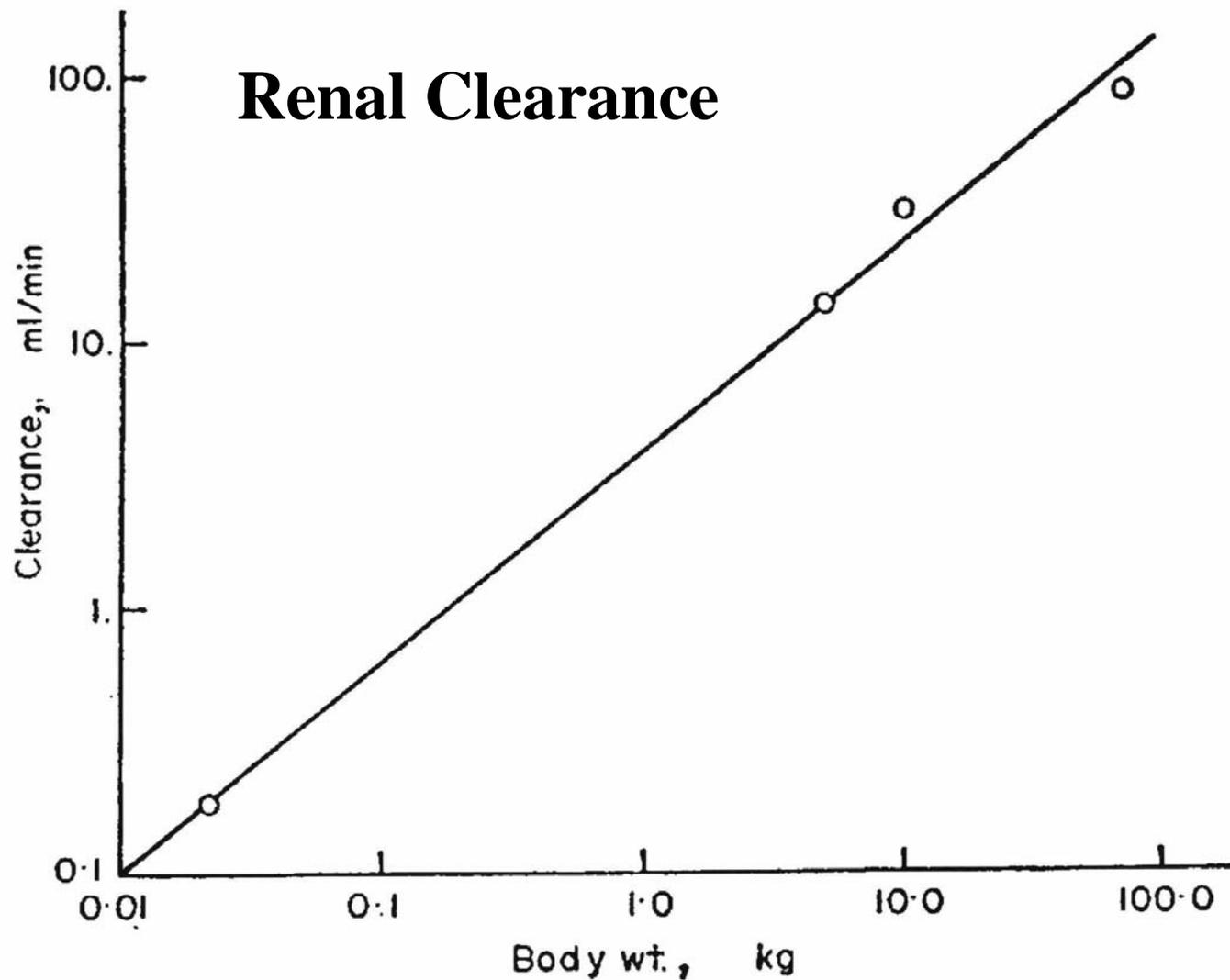
K = Michaelis constant, $\mu\text{g/ml}$

CL = non-metabolic clearance, ml/min

and the subscripts K and B refer to kidney and arterial blood, respectively.

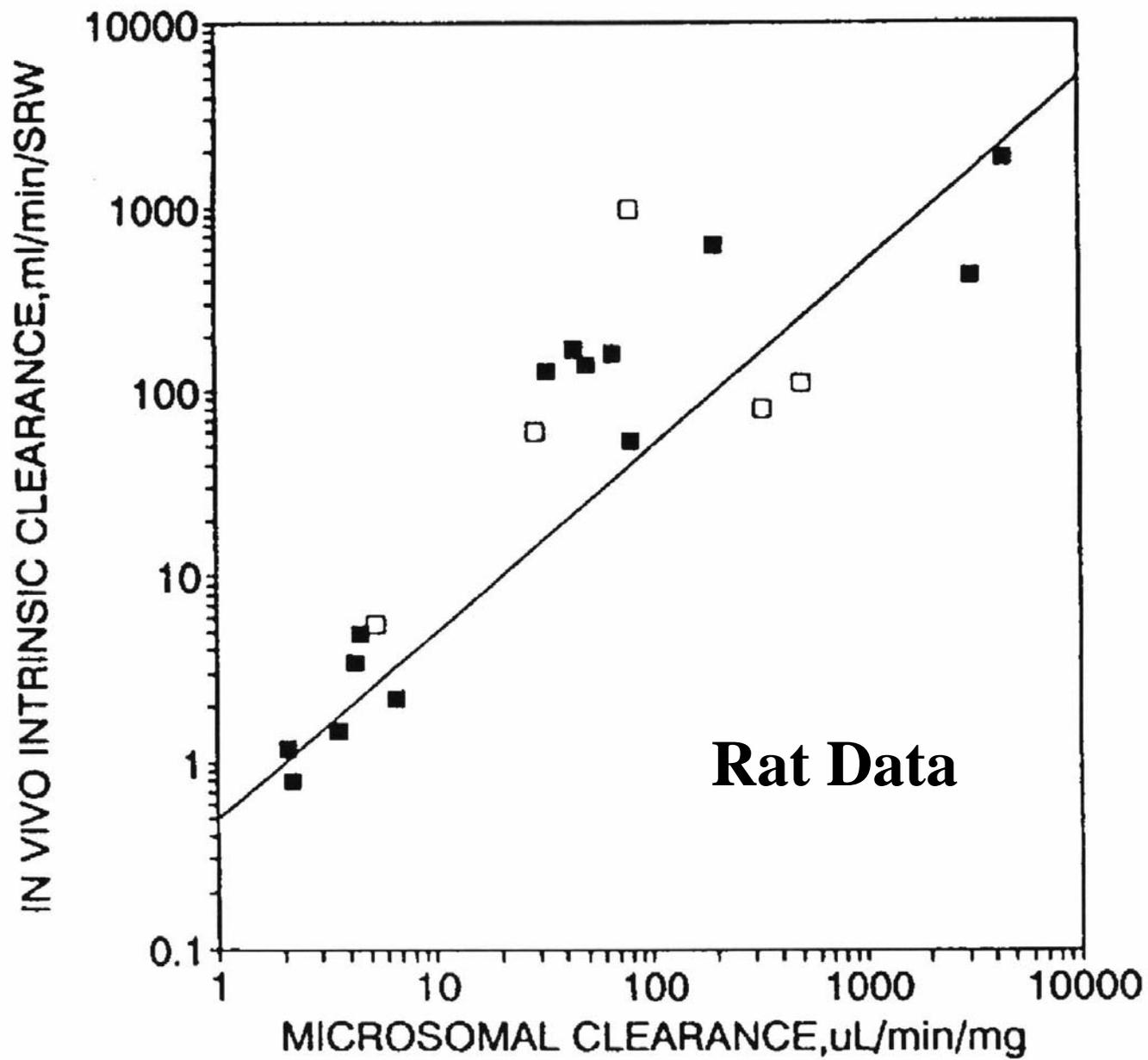


Dedrick RL et al, Biochem Pharmacol 21:1-16, 1972

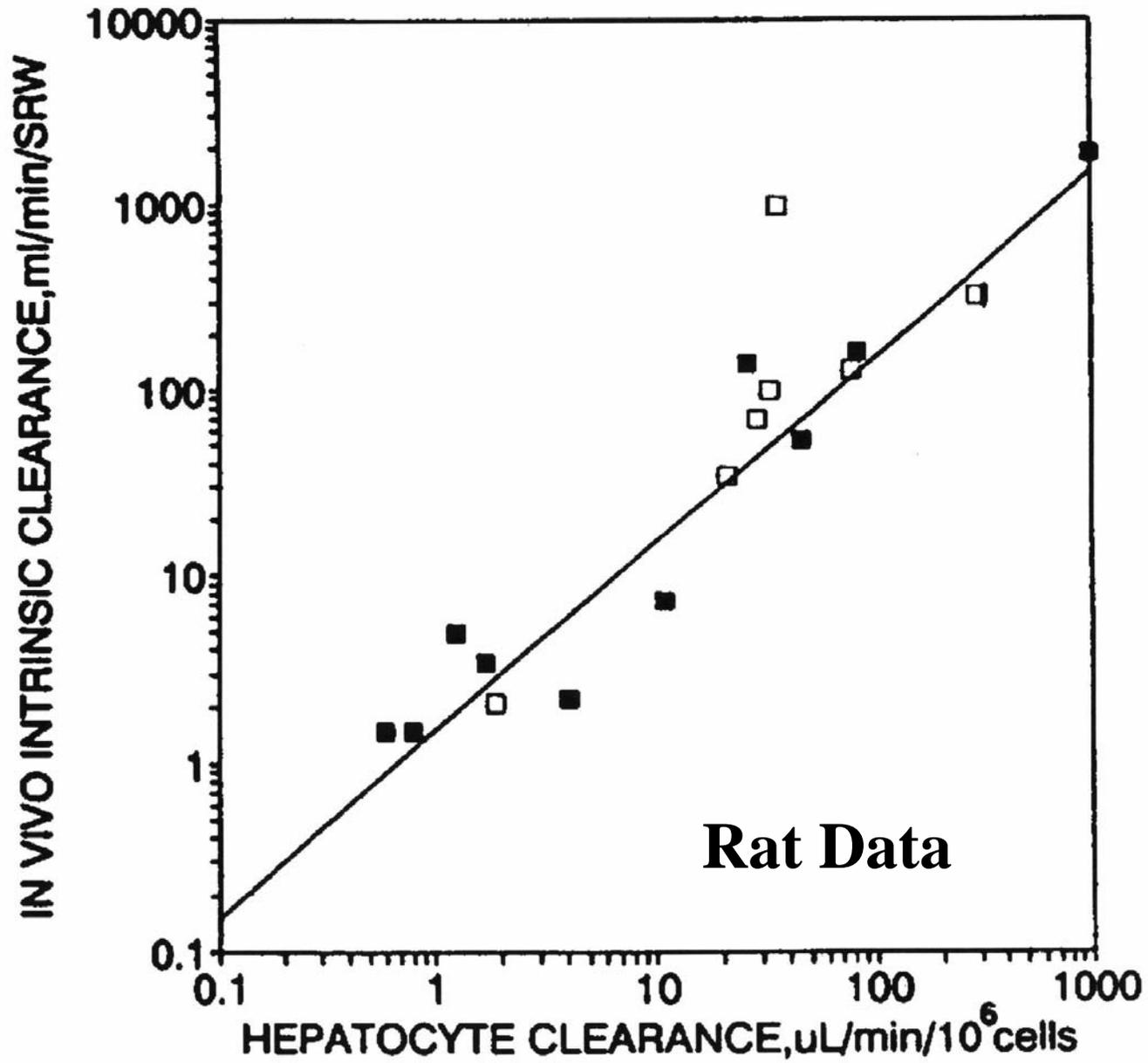


Kidney clearance of Ara-C and Ara-U vs body weight
for mice, monkeys, dogs and humans

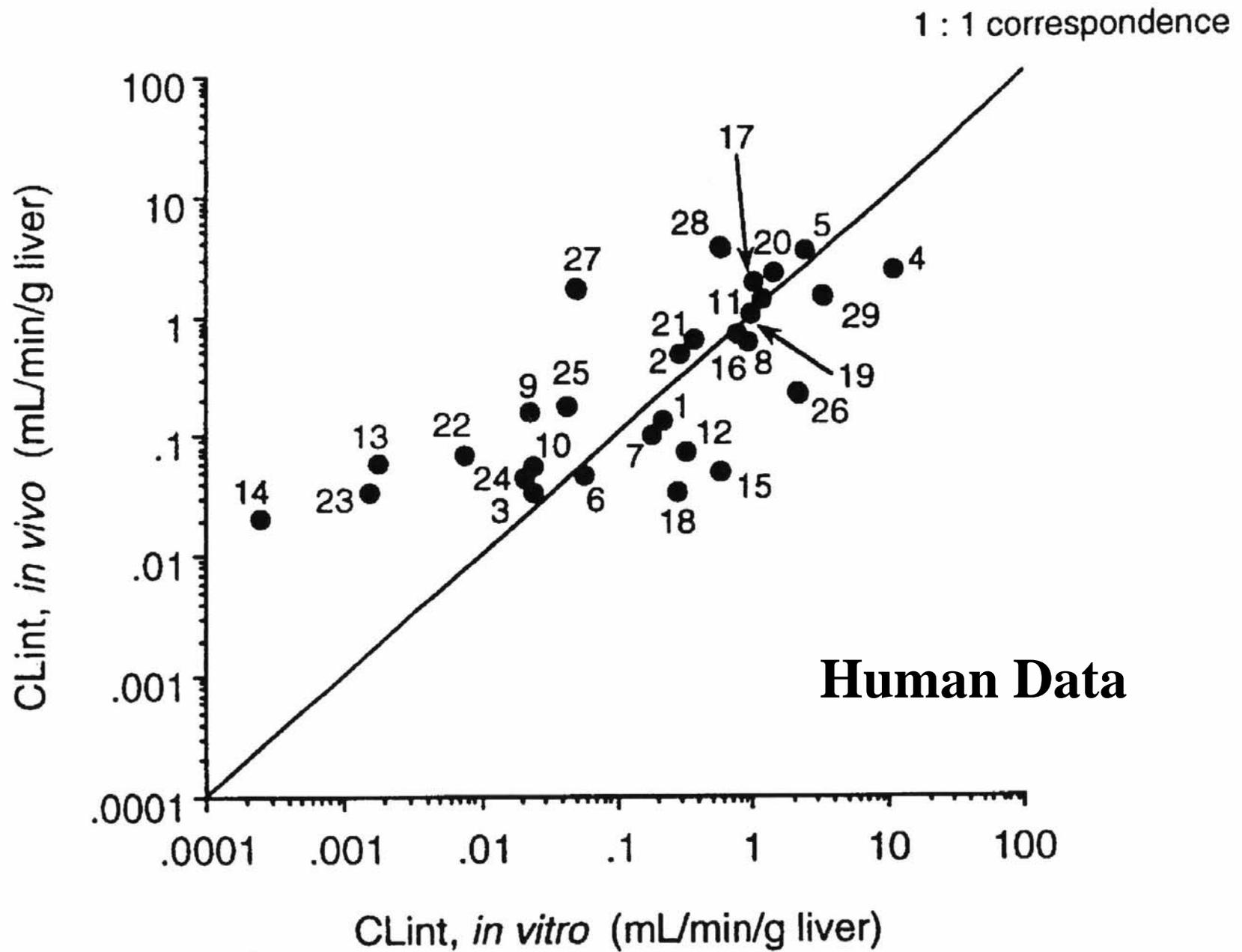
Dedrick RL et al, Biochem Pharmacol 22:2405-2417, 1973



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

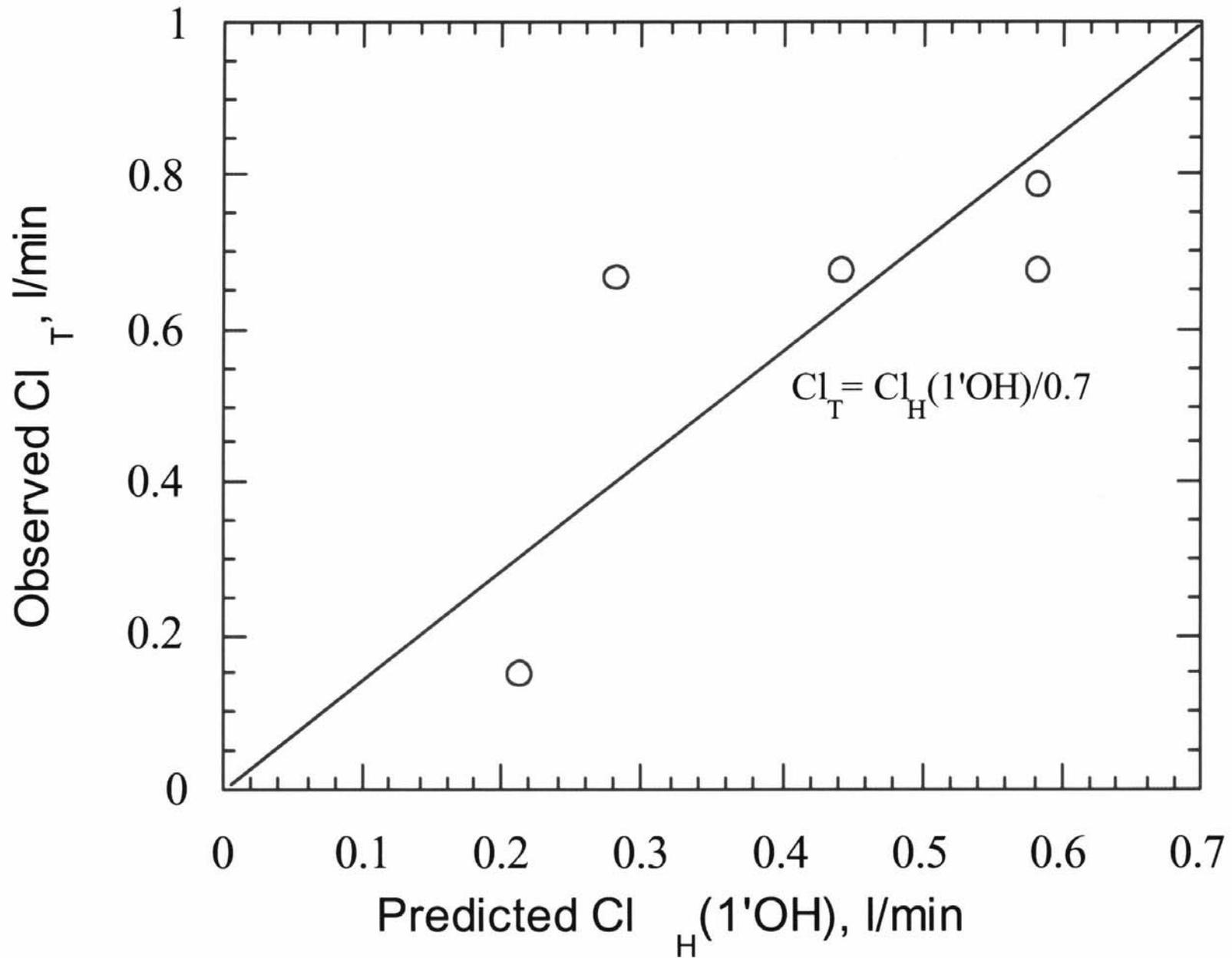


Houston JB, Biochem Pharmacol 47:1469-1479, 1994



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

Midazolam Clearance Human/Transplant



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