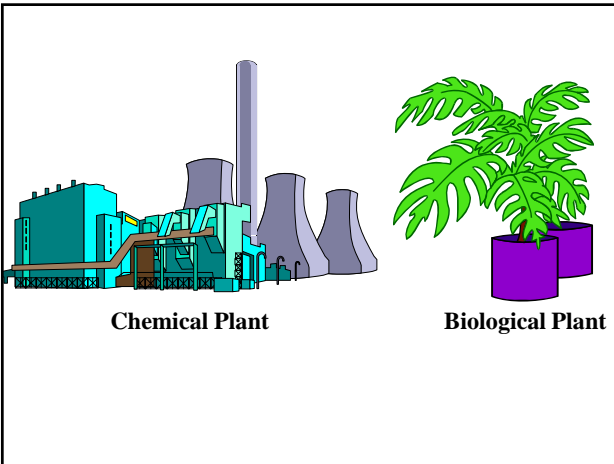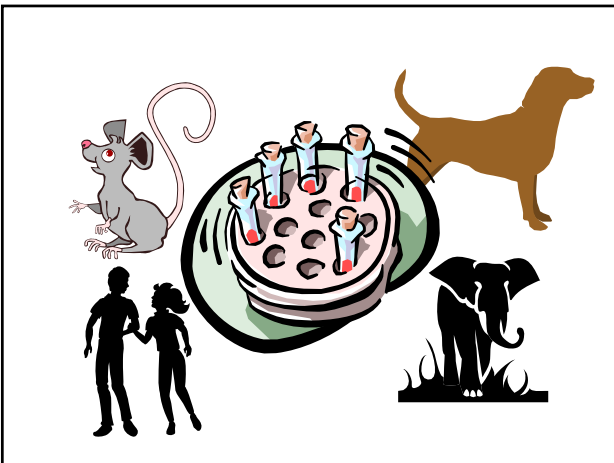# Animal Scale-Up

Robert L. Dedrick, Ph.D.

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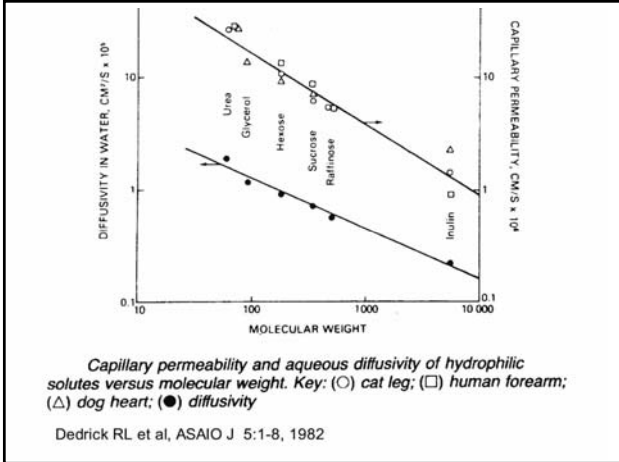Bioengineering, NIH**

April 1, 2010

Chemical Plant **Biological Plant**

Capillary permeability and aqueous diffusivity of hydrophilic solutes versus molecular weight. Key: (○) cat leg; (□) human forearm; (△) dog heart; (●) diffusivity
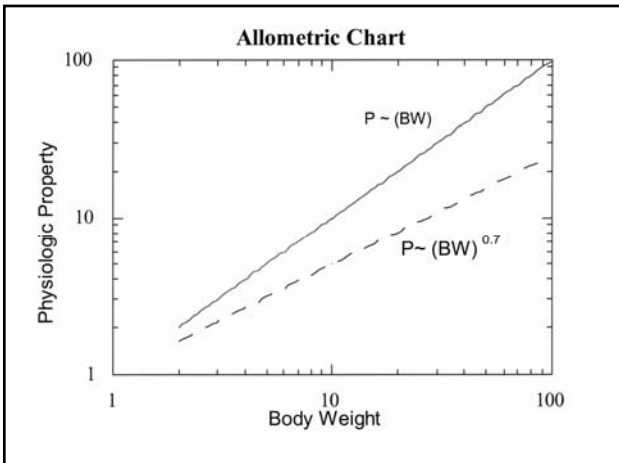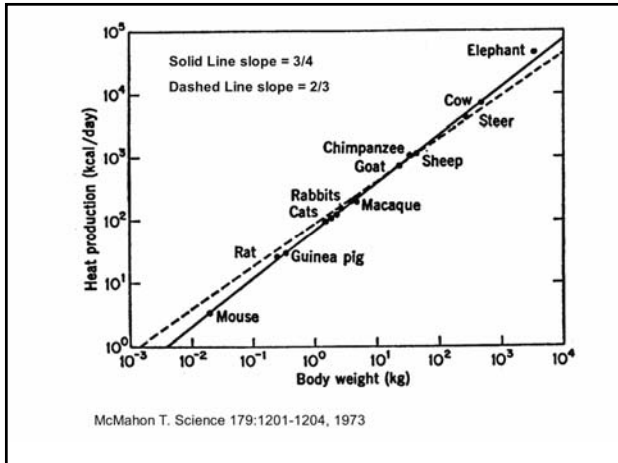
Dedrick RL et al, ASAIO J 5:1-8, 1982
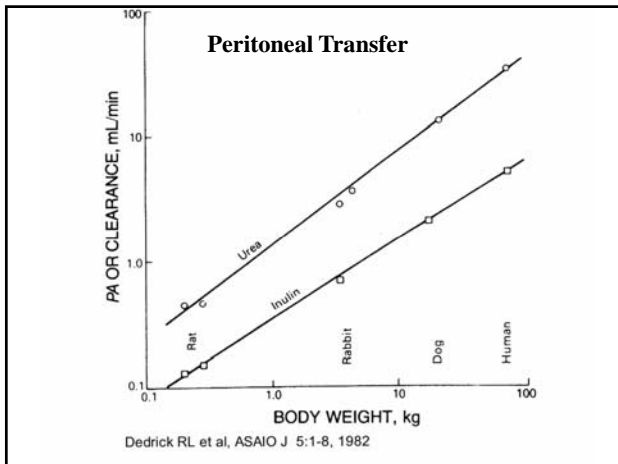
ALLOMETRIC EQUATION

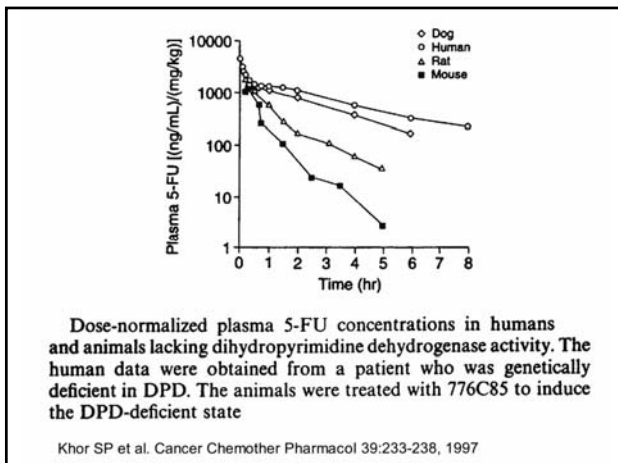$$P = a(BW)^m$$

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

Allometric Chart

$P \sim (BW)$

$P \sim (BW)^{0.7}$

Solid Line slope = 3/4
Dashed Line slope = 2/3

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

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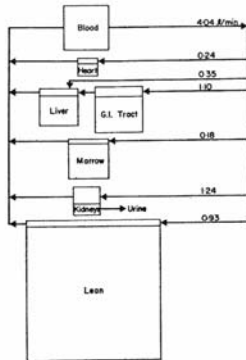
Khor SP et al. Cancer Chemother Pharmacol 39:233-238, 1997

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, 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.

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

Renal Clearance

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

Rat Data

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

Rat Data

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

Human Data

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

Midazolam Clearance Human/Transplant

$Cl_T = Cl_H(1'OH)/0.7$

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