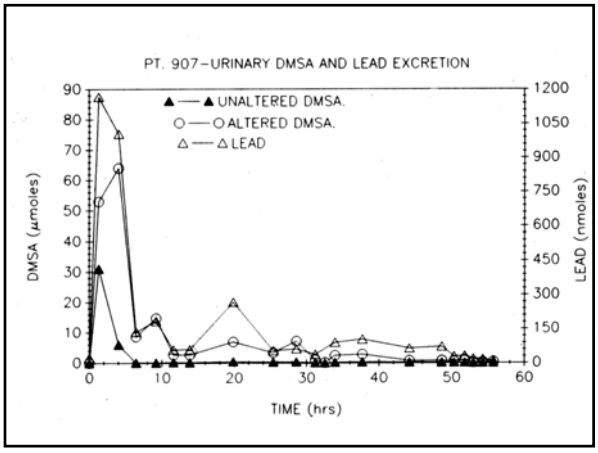
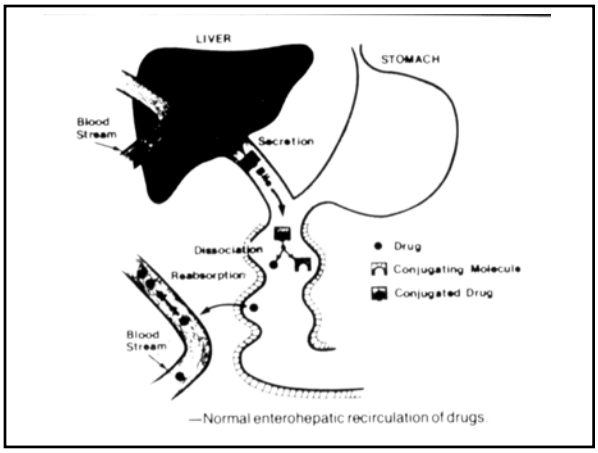
Drug Absorption, Distribution, Metabolism and Elimination: Part III

Joseph Graziano, Ph.D.





—Normal enterohepatic recirculation of drugs.

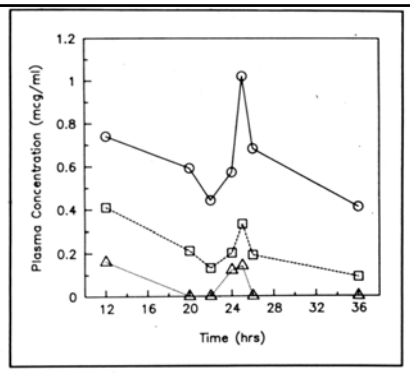


Figure 2. Plasma Concentration Profile of Sulindac (Δ) and its sulfone (O) and Sulfide (□) Metabolites During the 12 to 36 hour Period Following a 200 mg Dose to a Subject. Re-entry peaks are readily evident following consumption of breakfast at 22 Hours.

TABLE I

Examples of Compounds Excreted in Bile and Subject to Enterohepatic Cycling

Compound	Entity in Bile
Cholic acid	taurocholate/glycocholate
Testosterone	conjugates
Estradiol	N.R.†
Vitamin A	conjugates
Cefoperazone	N.R.
Chloramphenicol	glucuronide conjugate
Demeclocycline	N.R.
Nafcillin	N.R.
Rifamicin	N.R.
Digoxin	N.R.
Digitoxin	conjugates
Spironolactone	metabolites
Imipramine	parent & desmethyl metabolite
Indomethacin	glucuronide
Sulindac	glucuronides of parent & metabolites
Valproic acid	glucuronide
Ivermectin	N.R.

† N.R. = not reported.

Oral contraceptive failures reported to the British Committee on the Safety of Medicines in women taking antibiotics.

Number of failures	*Antibiotics*
3	Ampicillin
1	Ampicillin + fusidic acid
1	Ampicillin + tetracycline
1	Ampicillin + flucloxacillin
2	Amoxycillin
1	Talampicillin
1	Cephalexin + clindamycin
1	Phenoxymethylpenicillin + oxytetracycline
1	Phenoxymethylpenicillin
4	'Penicillin'
1	Streptomycin + rifampicin + isoniazid
2	Tetracycline
4	Oxytetracycline
1	Erythromycin
3	'Antibiotic'
1	Isoniazid
2	Dapsone
1	Nitrofurantoin
5	Co-trimoxazole

PHARMACOGENETICS AND GENOMICS

CYP2C19 genotype status and effect of omeprazole on intragastric pH in humans

Objective: Omeprazole is metabolized by genetically determined S-mephenytoin 4′-hydroxylase (CYP2C19) in the liver. This study aimed to determine whether the effect of omeprazole on intragastric pH depends on *CYP2C19* genotype status.

Methods: *CYP2C19* genotype status for 2 mutations associated with the poor metabolizer phenotype was determined by a polymerase chain reaction–restriction fragment length polymorphism method in 16 healthy volunteers. *Helicobacter pylori* status was determined by serology and the [^{13}C]urea breath test. After a single oral administration of 20 mg omeprazole or a placebo, intragastric pH values were recorded for 24 hours. Plasma levels of omeprazole and its 2 metabolites and gastrin were measured before and 1, 2, 3, 5, 7, 10, and 24 hours after administration.

Results: Fifteen of the 16 subjects were *H pylori* negative. Five of the 15 subjects were homozygous extensive metabolizers, 4 were heterozygous extensive metabolizers, and 6 were poor metabolizers. After omeprazole administration, significant differences in mean intragastric pH values and plasma levels of gastrin, omeprazole and its metabolites were observed among the 3 groups, whereas no significant differences in these parameters were observed with the placebo administration.

Conclusions: The effect of omeprazole on intragastric pH significantly depends on *CYP2C19* genotype status. The genotyping test of CYP2C19 may be useful for an optimal prescription of omeprazole. (Clin Pharmacol Ther 1999;65:552-61.)

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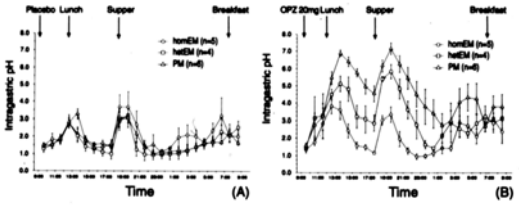


Figure 1. Mean ± SE intragastric pH values as a function of CYP2C19 genotype status for administration of placebo **(A)** or 20 mg omeprazole (OPZ; **B**). When placebo was administered, the mean intragastric pH values were substantially the same among the 3 groups **(A)**. The mean intragastric pH values differed significantly ($P = .0001$) among 3 groups when 20 mg omeprazole was administered **(B)**. homEM, Homozygous extensive metabolizer; hetEM, heterozygous extensive metabolizer; PM, poor metabolizer.

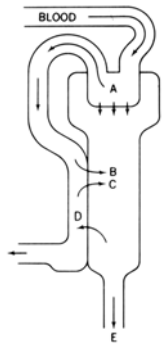


Fig. 11–1. Schematic representation of renal excretion of drugs depicting glomerular filtration of plasma water and unbound drug (A), active tubular secretion of organic acids (B) and bases (C), reabsorption of lipid-soluble drugs (D), and urinary excretion (E).

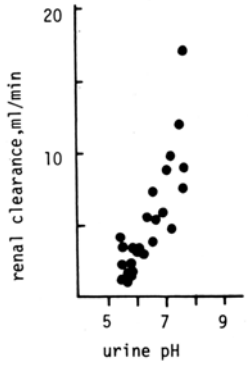


Fig. 11–2. Effect of urine pH on the renal clearance of sulfamethoxazole. (Data from Vree, T.B., et al.[6])

Table 5-2 Effect of Urine pH on Renal Clearance for Drugs that Undergo Tubular Resorption

Bases	Acids
CLEARED RAPIDLY BY MAKING URINE MORE ACIDIC	CLEARED RAPIDLY BY MAKING URINE MORE ALKALINE
amphetamine	acetazolamide
chloroquine	nitrofurantoin
imipramine	phenobarbital
levophanol	probenecid
mecamylamine	salicylates
quinine	sulfathiazole

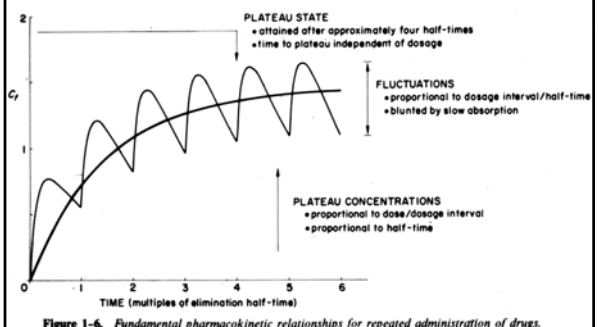


Figure 1-6. *Fundamental pharmacokinetic relationships for repeated administration of drugs.*

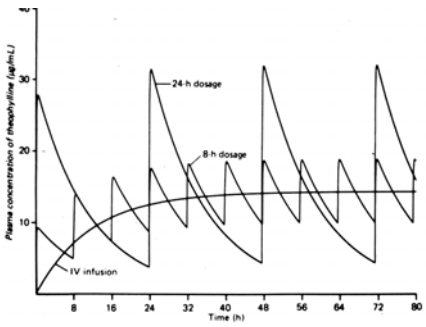
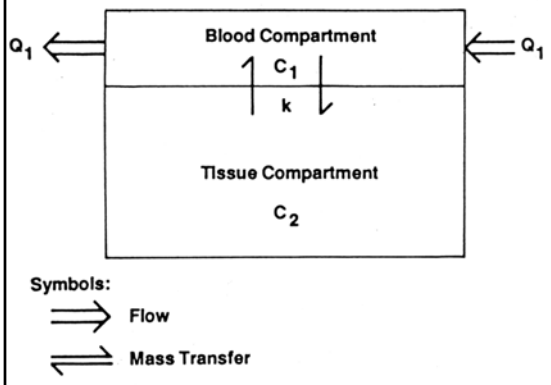
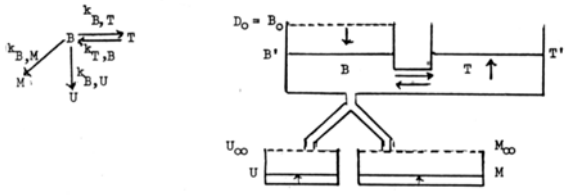


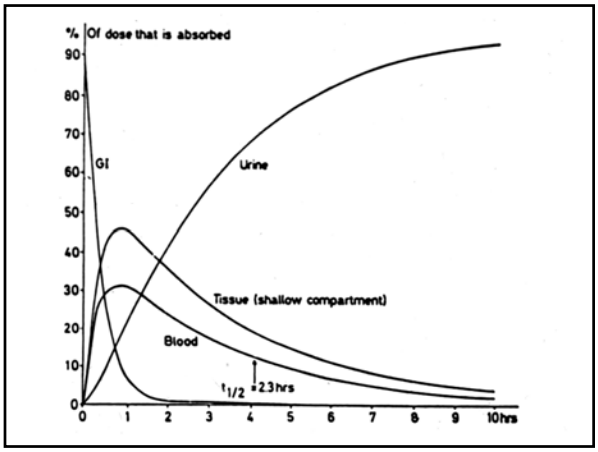
Figure 3–6. Relationship between frequency of dosing and maximum and minimum plasma concentrations when a steady-state theophylline plasma level of 15 μg/mL is desired. The smoothly rising line shows the plasma concentration achieved with an intravenous infusion of 43.2 mg/h. The doses for 8-hourly administration are 340 mg; for 24-hourly administration, 1020 mg. In each of the 3 cases, the mean steady-state plasma concentration is 15 μg/mL.

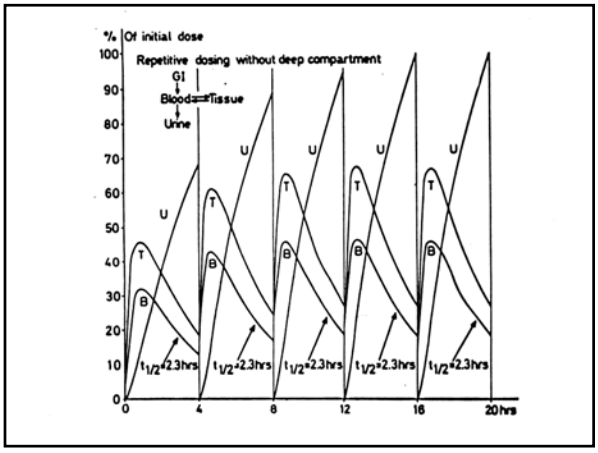


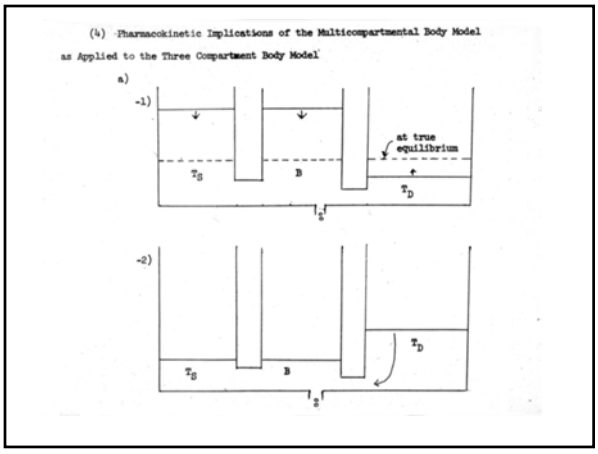
VIII The Two Compartment Body Model

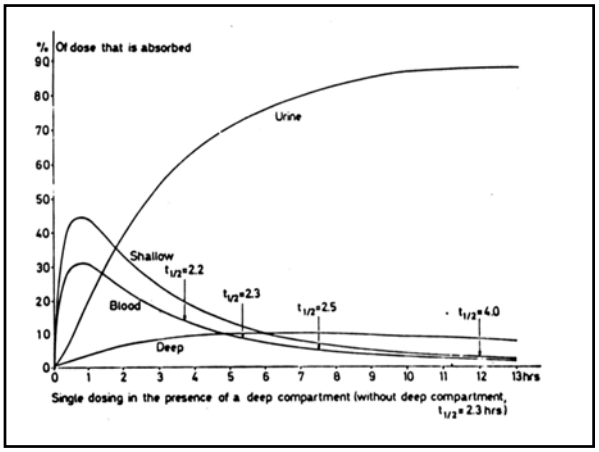
(1) Model (for intravenous administration of a dose $B_o = D_o$):

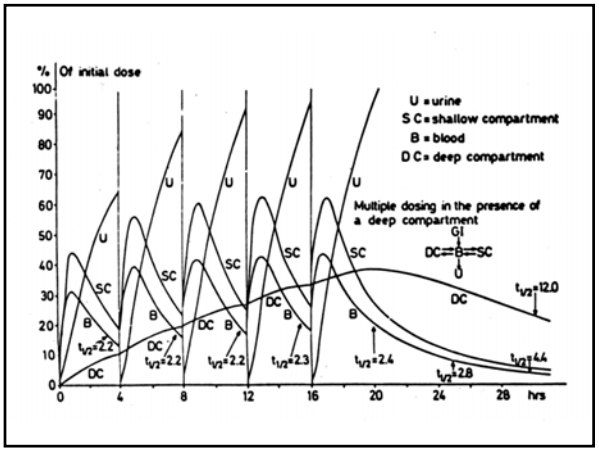



% Of dose that is absorbed
90
80
70
60
50
40
30
20
10
0
GI
Urine
Tissue (shallow compartment)
Blood
t1/2 =2.3hrs
0 1 2 3 4 5 6 7 8 9 10hrs


% Of initial dose
100
90
80
70
60
50
40
30
20
10
0
Repetitive dosing without deep compartment
GI
Blood⇌Tissue
Urine
U
T
B
t1/2=2.3hrs
0 4 8 12 16 20hrs


(4) Pharmacokinetic Implications of the Multicompartmental Body Model
as Applied to the Three Compartment Body Model
a)
-1)
at true
equilibrium
T_S
B
T_D
t_1
-2)
T_D
T_S
B
t_2





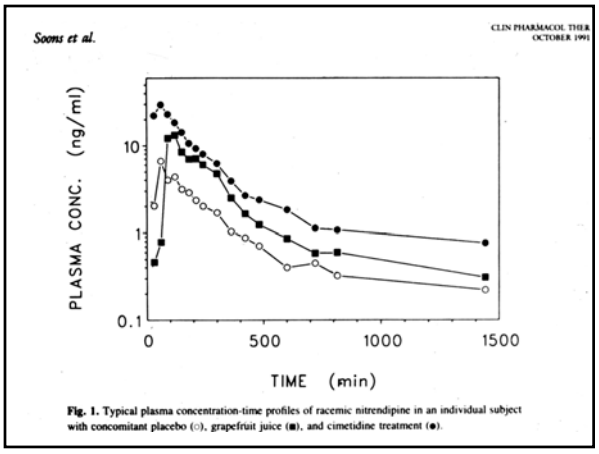
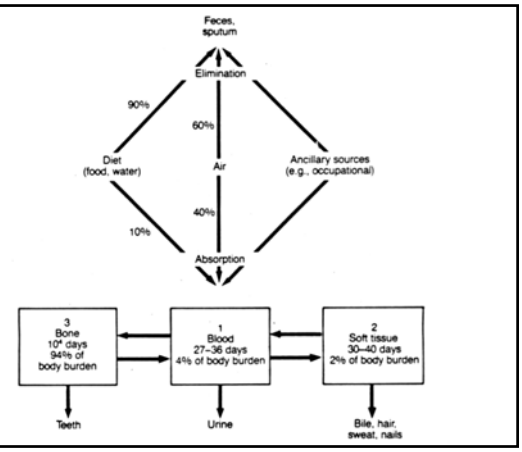


Fig. 1. Typical plasma concentration-time profiles of racemic nitrendipine in an individual subject with concomitant placebo (○), grapefruit juice (■), and cimetidine treatment (●).



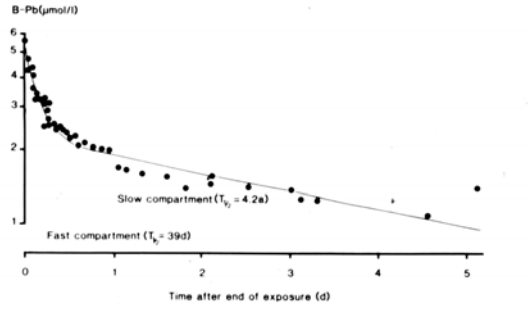


Fig. 2. Decay of blood lead level (logarithmic) after end of exposure in an ex-lead worker. A linear two-compartment model was fitted to the data. A "background" of 0.3 µmol/l has been subtracted. Biological half-times ($T_{1/2}$) for the compartments are given.

TABLE 1 Selected Mechanisms and Examples of Drugs Showing Saturable Kinetic Behavior

Mechanism	Drug example
Absorption	
Saturable transport in gut wall	Riboflavin
Saturable metabolism during first pass	Propranolol
Distribution	
Saturable plasma protein binding	Disopyramide
Excretion	
Active tubular secretion	Penicillin
Active tubular reabsorption	Ascorbic acid
Metabolism	
Capacity-limited (saturable) metabolism	Phenytoin
Cofactor supply limitation	Salicylamide

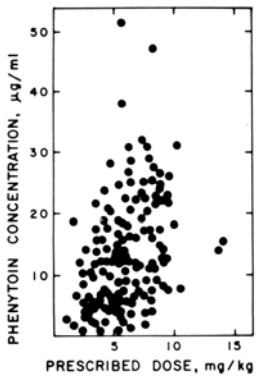


Fig. 12–2. Relationship between the steady-state plasma concentration of phenytoin in epileptic patients and the prescribed daily dose. (Data from Lund, L.[1])