EFFECTS OF RENAL DISEASE ON PHARMACOKINETICS

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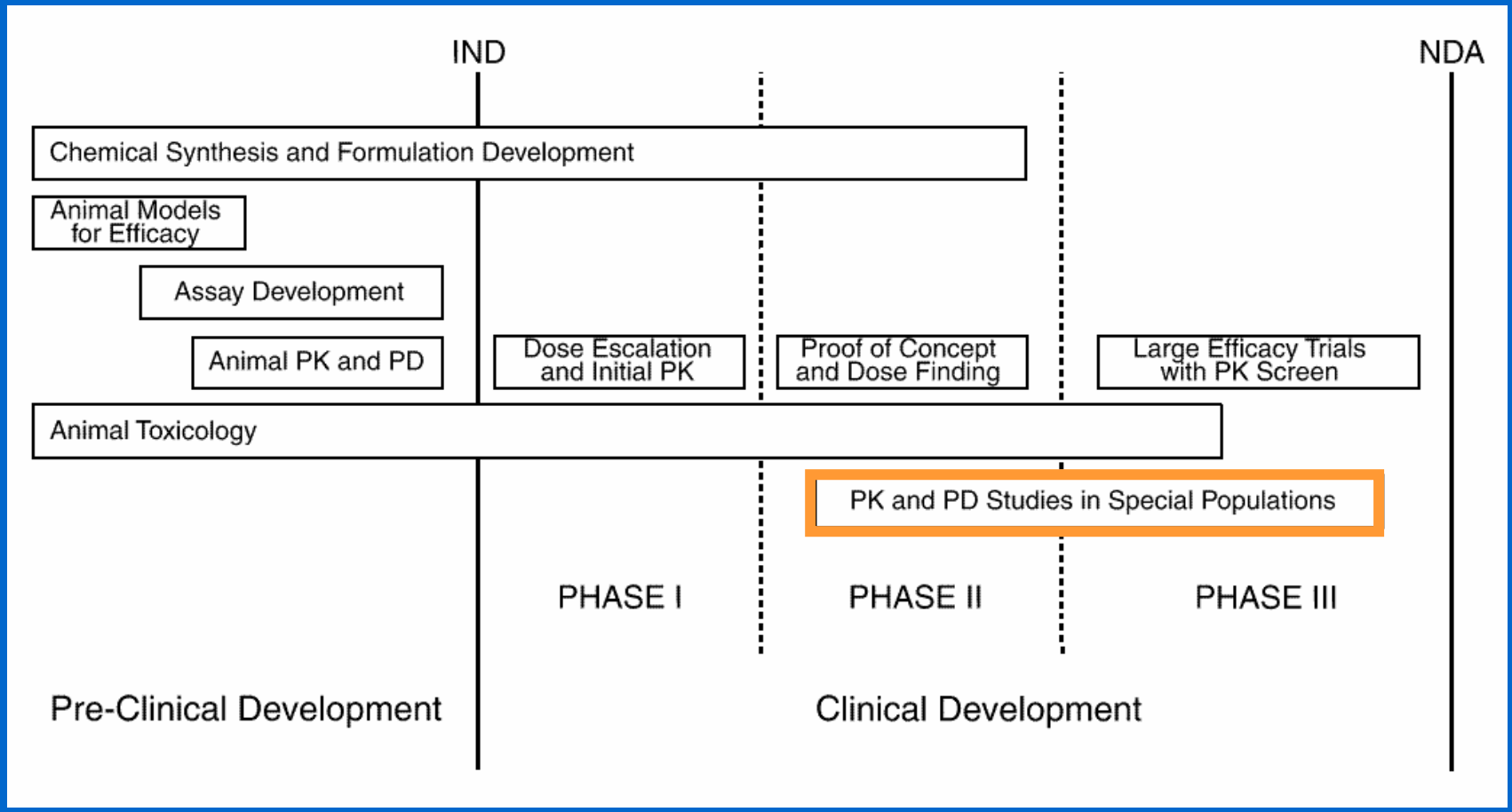
TIMING OF PK & PD STUDIES



FDA GUIDANCE FOR INDUSTRY

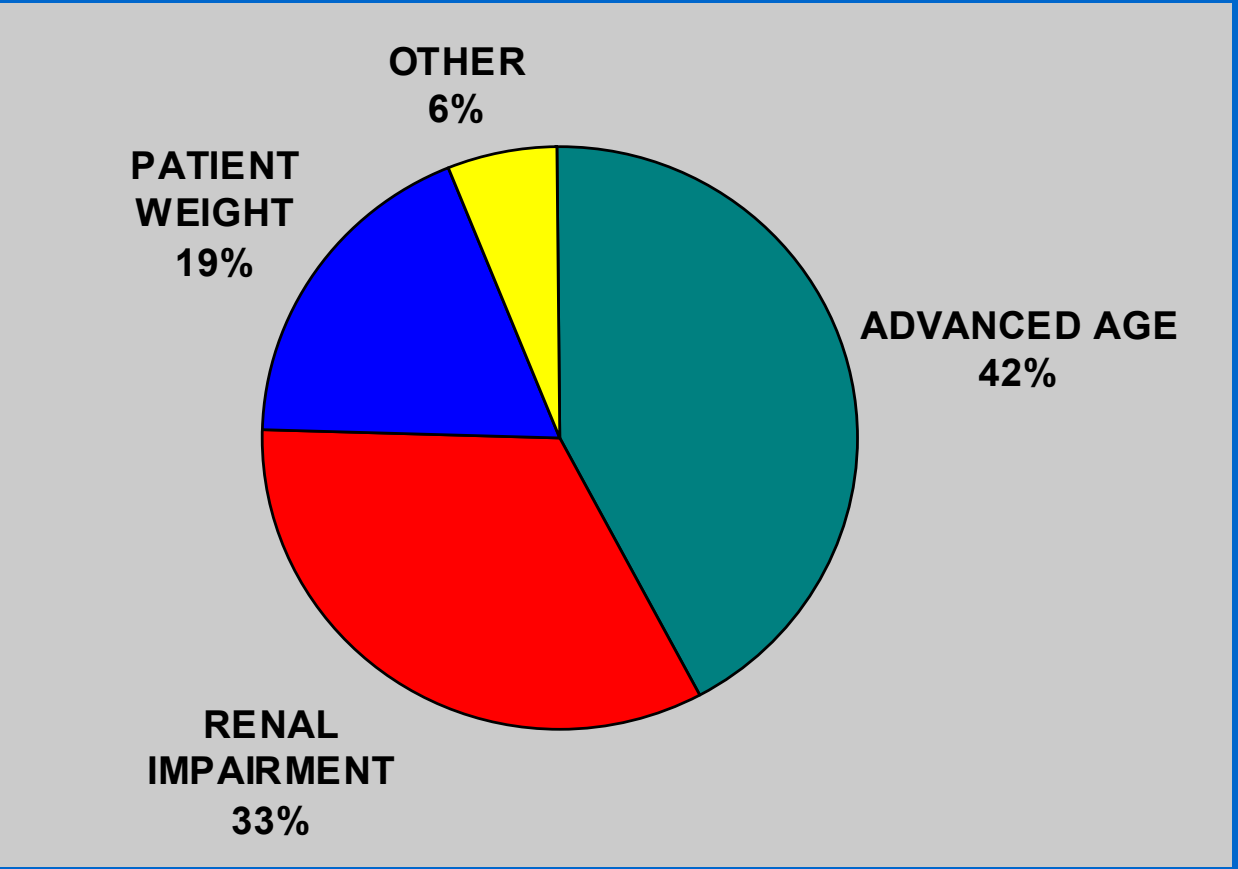
PHARMACOKINETICS IN PATIENTS WITH IMPAIRED RENAL FUNCTION - STUDY DESIGN DATA ANALYSIS, AND IMPACT ON DOSING AND LABELING

AVAILABLE AT:
http://www.fda.gov/cder/guidance/index.htm

PATIENT CHARACTERISTICS IMPACT DRUG RESPONSE

PHARMACEUTICAL PHASE	PHARMACOKINETIC PHASE	PHARMACODYNAMIC PHASE

PATHOPHYSIOLOGIC FACTORS NOT ACCOUNTED FOR IN DRUG DOSING*



* Lesar TS, Briceland L, Stein DS. JAMA 1997;277:312-7.

GOALS OF RENAL DISEASE EFFECTS LECTURE

- DOSE ADJUSTMENT IN PATIENTS WITH RENAL IMPAIRMENT
- EFFECT OF RENAL DISEASE ON RENAL ELIMINATION
- EFFECT OF RENAL DISEASE ON DRUG METABOLISM
- EFFECT OF RENAL DISEASE ON DRUG DISTRIBTION
- EFFECT OF RENAL DISEASE ON DRUG ABSORPTION

STEADY STATE CONCENTRATION

CONTINUOUS INFUSION:

$$C_{SS} = \frac{I}{CL_E}$$

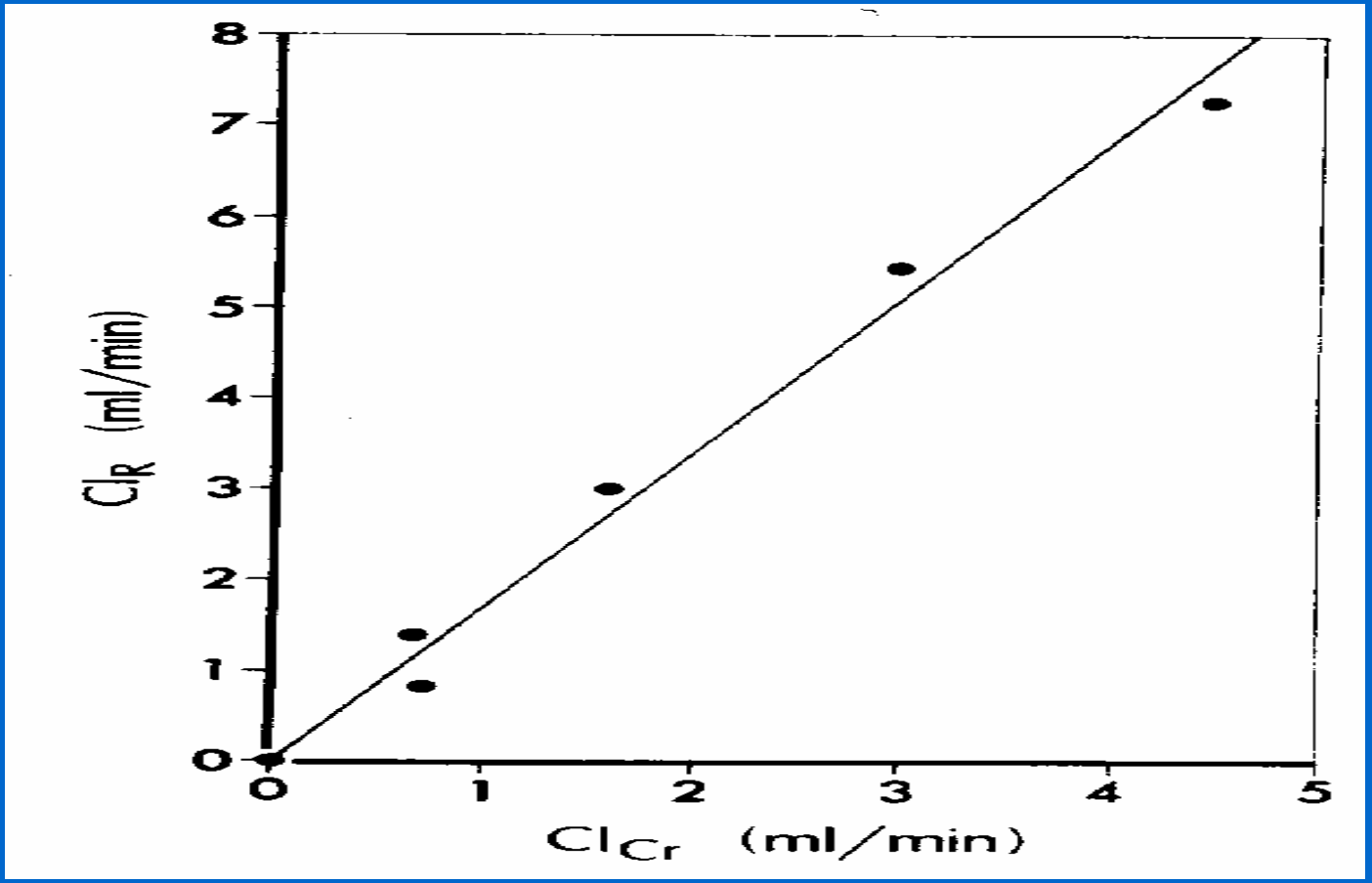
INTERMITTENT DOSING:

$$\overline{C}_{SS} = \frac{DOSE/\tau}{CL_E}$$

ADDITIVITY OF CLEARANCES

$$Cl_E = Cl_R + Cl_{NR}$$

CL_R VS. CL_{CR} IS LINEAR

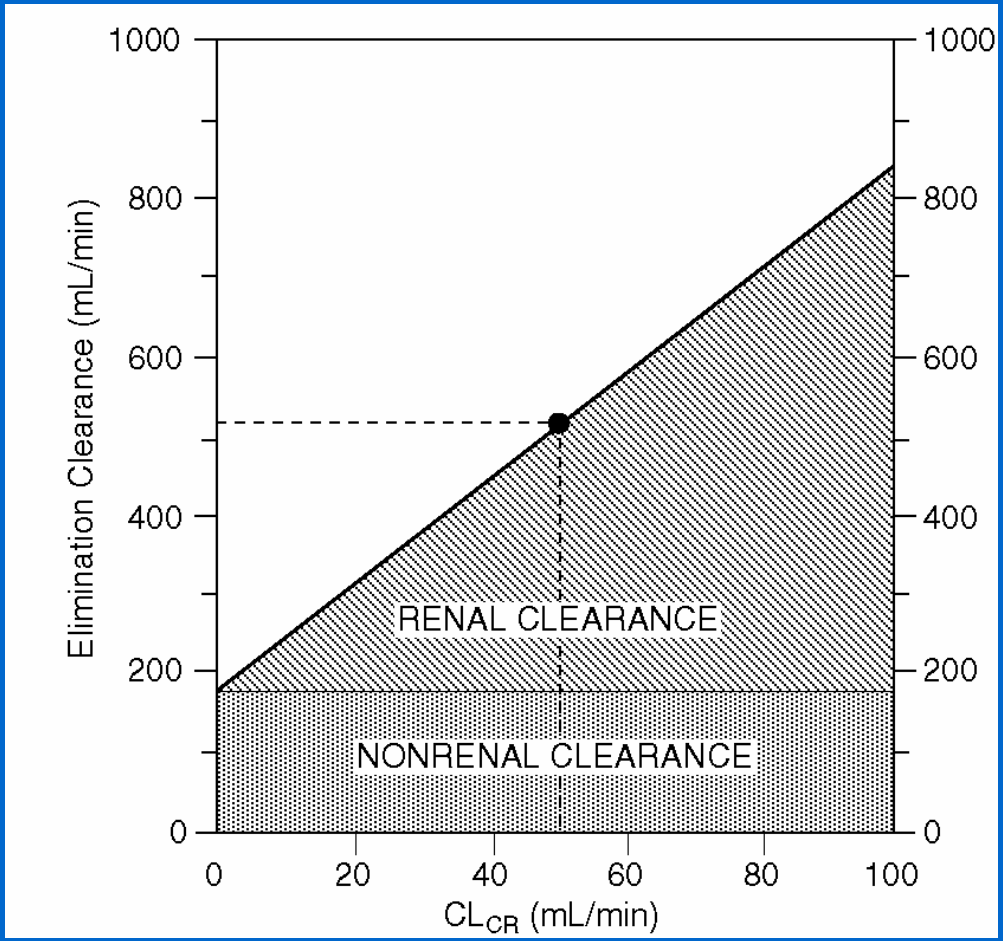


* From: Stec GP, et al. Clin Pharmacol Ther 1979;26:618-28.

ADDITIVITY OF CLEARANCES

$$Cl_E = Cl_R + Cl_{NR}$$

NOMOGRAM FOR CIMETIDINE DOSING*



*From: Atkinson AJ Jr, Craig RM. Therapy of peptic ulcer disease.

KEY ASSUMPTIONS OF DETTLI METHOD

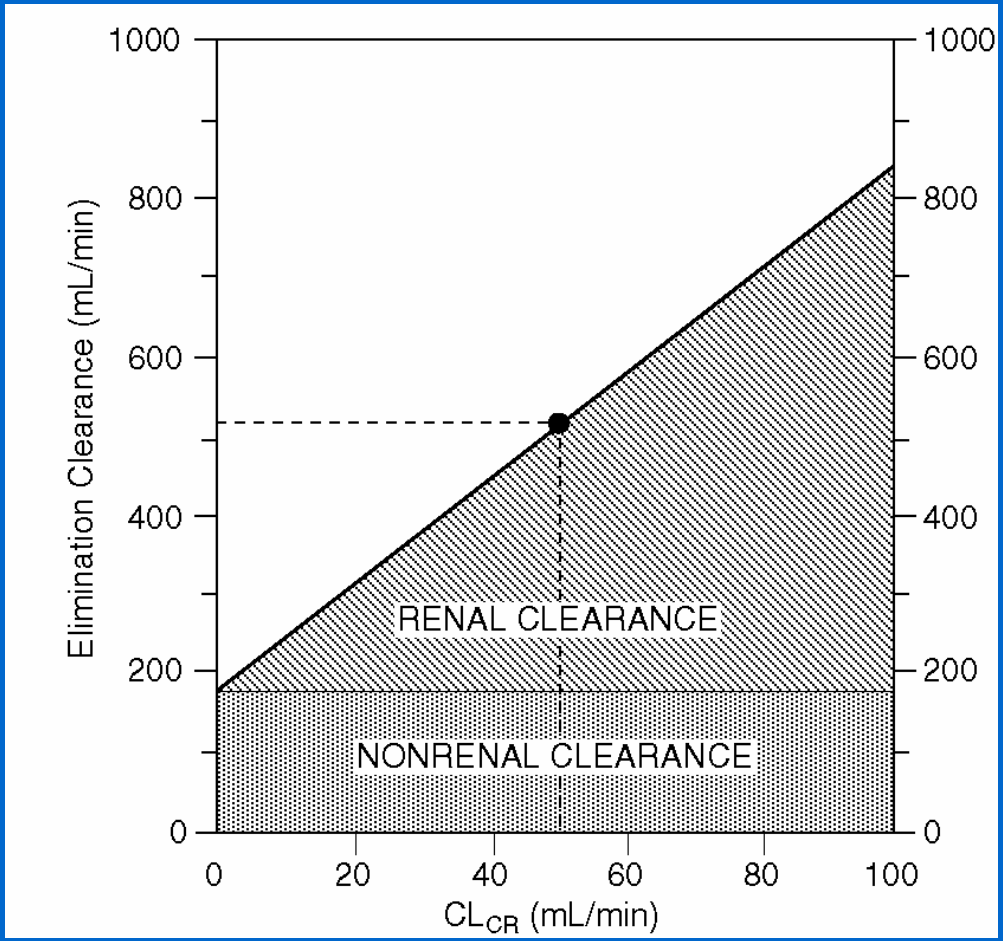
- CL_{NR} REMAINS CONSTANT WHEN RENAL FUNCTION IS IMPAIRED
- CL_R DECLINES IN LINEAR FASHION WITH CL_{CR}

LABELING FOR CIMETIDINE*

- **DOSAGE ADJUSTMENT**
  1/2 NORMAL DOSE IF CL_{CR} < 30 mL/min
- **PHARMACOKINETICS**
  FOLLOWING I.V. OR I.M. ADMINISTRATION, ” 75% OF DRUG IS RECOVERED FROM THE URINE AFTER 24 hr AS PARENT COMPOUND

*** Physician’s Desk Reference. 54th edition, 2000.**

NOMOGRAM FOR CIMETIDINE DOSING*



*From: Atkinson AJ Jr, Craig RM. Therapy of peptic ulcer disease.

ELIMINATION HALF-LIFE

$$t_{1/2} = \frac{0.693 \bullet V_{d(area)}}{CL_E}$$

MECHANISMS OF RENAL ELIMINATION

I. GLOMERULAR FILTRATION

- AFFECTS ALL DRUGS & METABOLITES OF APPROPRIATE MOLECULAR SIZE
- INFLUENCED BY PROTEIN BINDING (f = FREE FRACTION)

DRUG FILTRATION RATE = GFR x f x [DRUG]

II. RENAL TUBULAR SECRETION

- NOT INFLUENCED BY PROTEIN BINDING
- MAY BE AFFECTED BY COMPETITION WITH OTHER DRUGS, ETC.

EXAMPLES:

ACTIVE DRUGS:	ACIDS – PENICILLIN
	BASES – PROCAINE AMIDE
METABOLITES:	GLUCURONIDES, HIPPURATES, ETC.

III. REABSORPTION BY NON-IONIC DIFFUSION

- AFFECTS WEAK ACIDS & WEAK BASES
- ONLY IMPORTANT IF EXCRETION OF FREE DRUG IS MAJOR ELIMINATION PATH

EXAMPLES:

WEAK ACIDS:	PHENOBARBITAL
WEAK BASES:	QUINIDINE

IV. ACTIVE REABSORPTION

- AFFECTS IONS, NOT PROVED FOR OTHER DRUGS

EXAMPLES:

HALIDES:	FLUORIDE, BROMIDE
ALKALINE METALS:	LITHIUM

RESTRICTIVE VS. NONRESTRICTIVE ELIMINATION

RESTRICTIVE:

CLEARANCE DEPENDS ON PROTEIN BINDING ($CL = f_U \bullet CL_{int}$)

NONRESTRICTIVE:

CLEARANCE INDEPENDENT OF PROTEIN BINDING ($CL = Q$)

GOALS OF RENAL DISEASE EFFECTS LECTURE

- **EFFECT OF RENAL DISEASE ON DRUG METABOLISM**

- **EXAMPLES:**

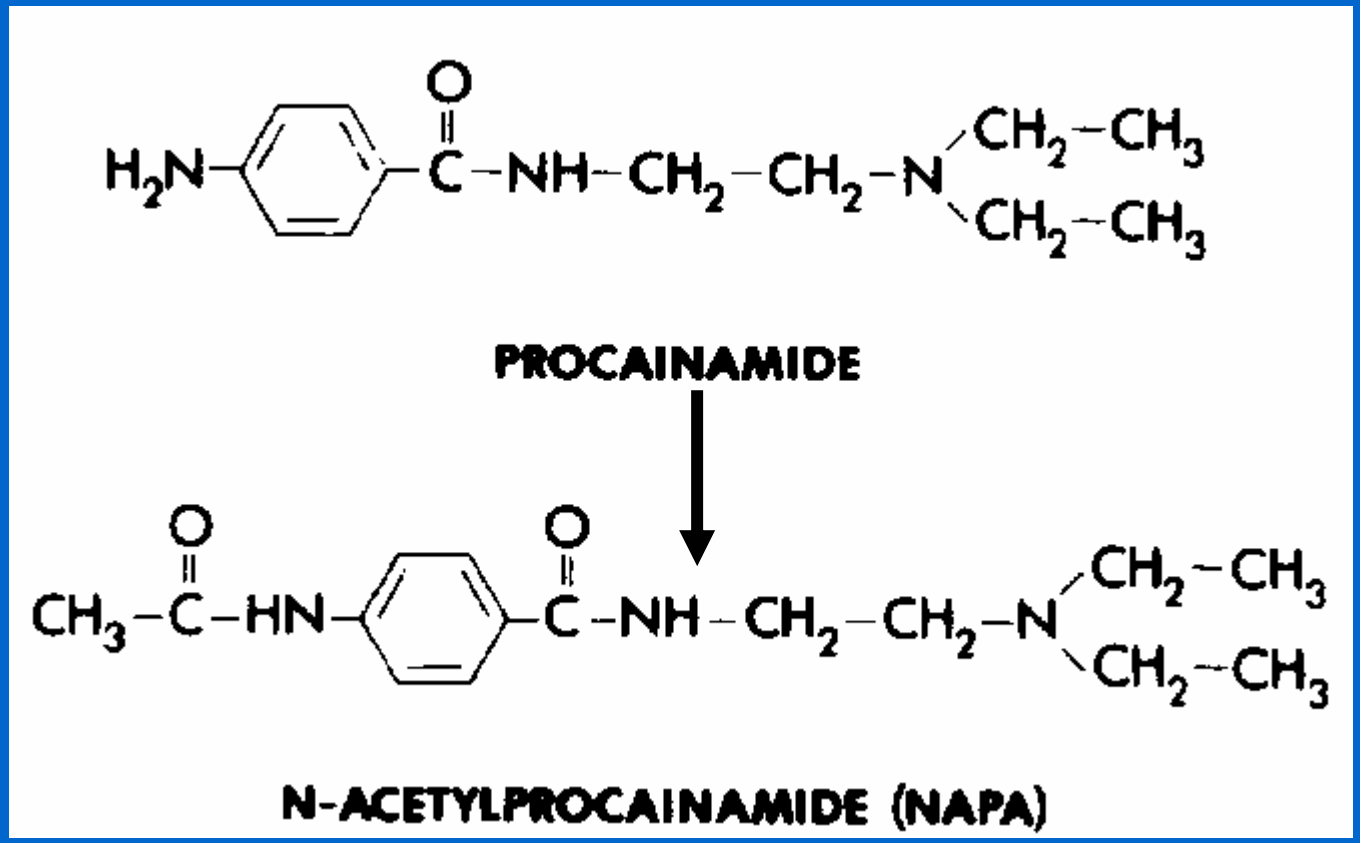
  PROCAINIMIDE - ACETYLATION

  PHENYTOIN - HYDROXYLATION

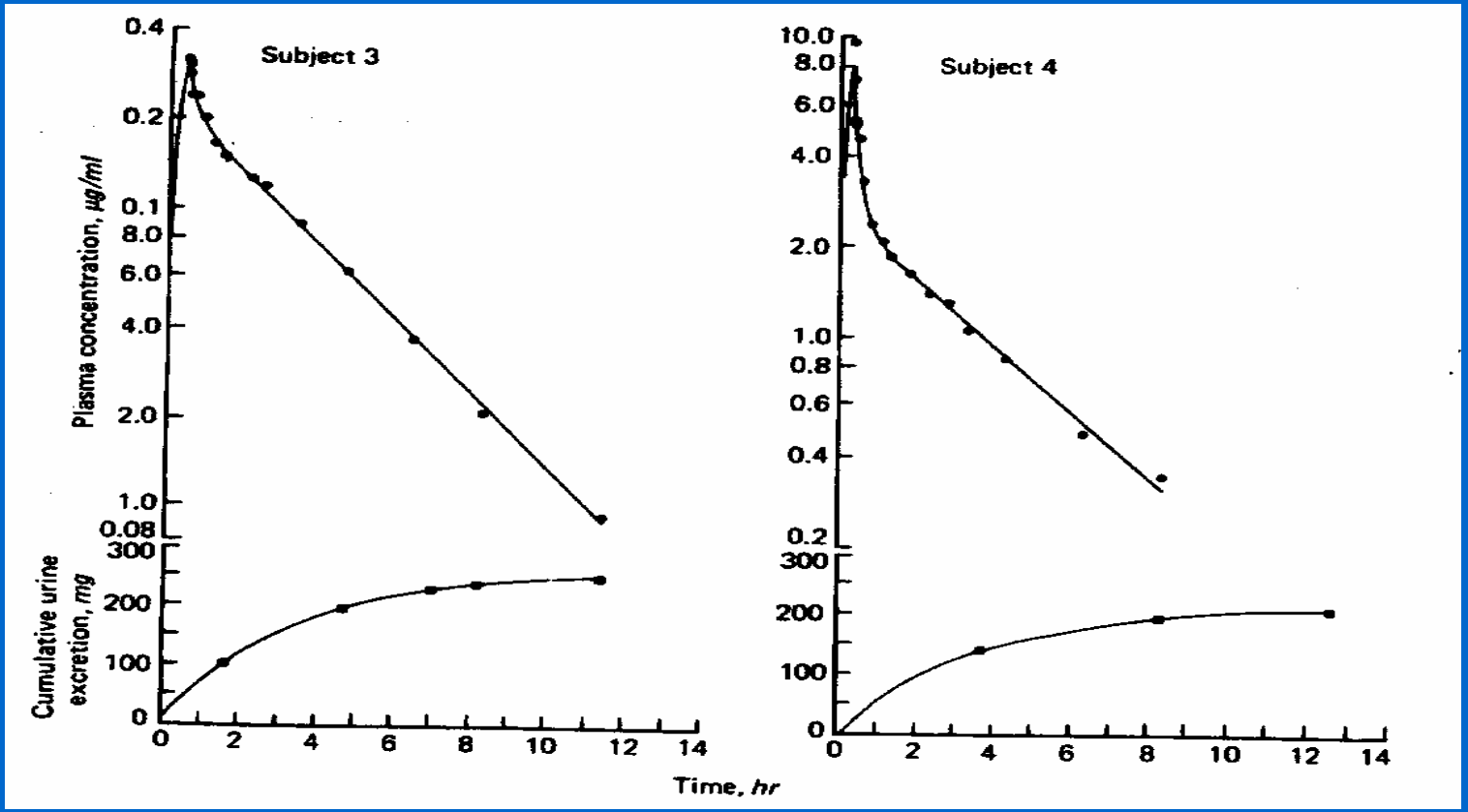
EFFECT OF RENAL DISEASE ON DRUG METABOLISM

	EXAMPLE	METABOLIC CLEARANCE
I. OXIDATIONS	PHENYTOIN	NORMAL OR INCREASED
II. REDUCTIONS	HYDROCORTISONE	SLOWED
III. HYDROLYSES		
• PLASMA ESTERASE	PROCAINE	SLOWED
• PLASMA PEPTIDASE	ANGIOTENSIN	NORMAL
• TISSUE PEPTIDASE	INSULIN	SLOWED
IV SYNTHESES		
• GLUCURONIDE FORMATION	HDYROCORTISONE	NORMAL
• ACETYLATION	PROCAINAMIDE	SLOWED
• GLYCINE CONJUGATION	PAS	SLOWED
• O-METHYLATION	METHYLDOPA	NORMAL
• SULFATE CONJUGATION	ACETAMINOPHEN	NORMAL

PROCAINAMIDE ACETYLATION

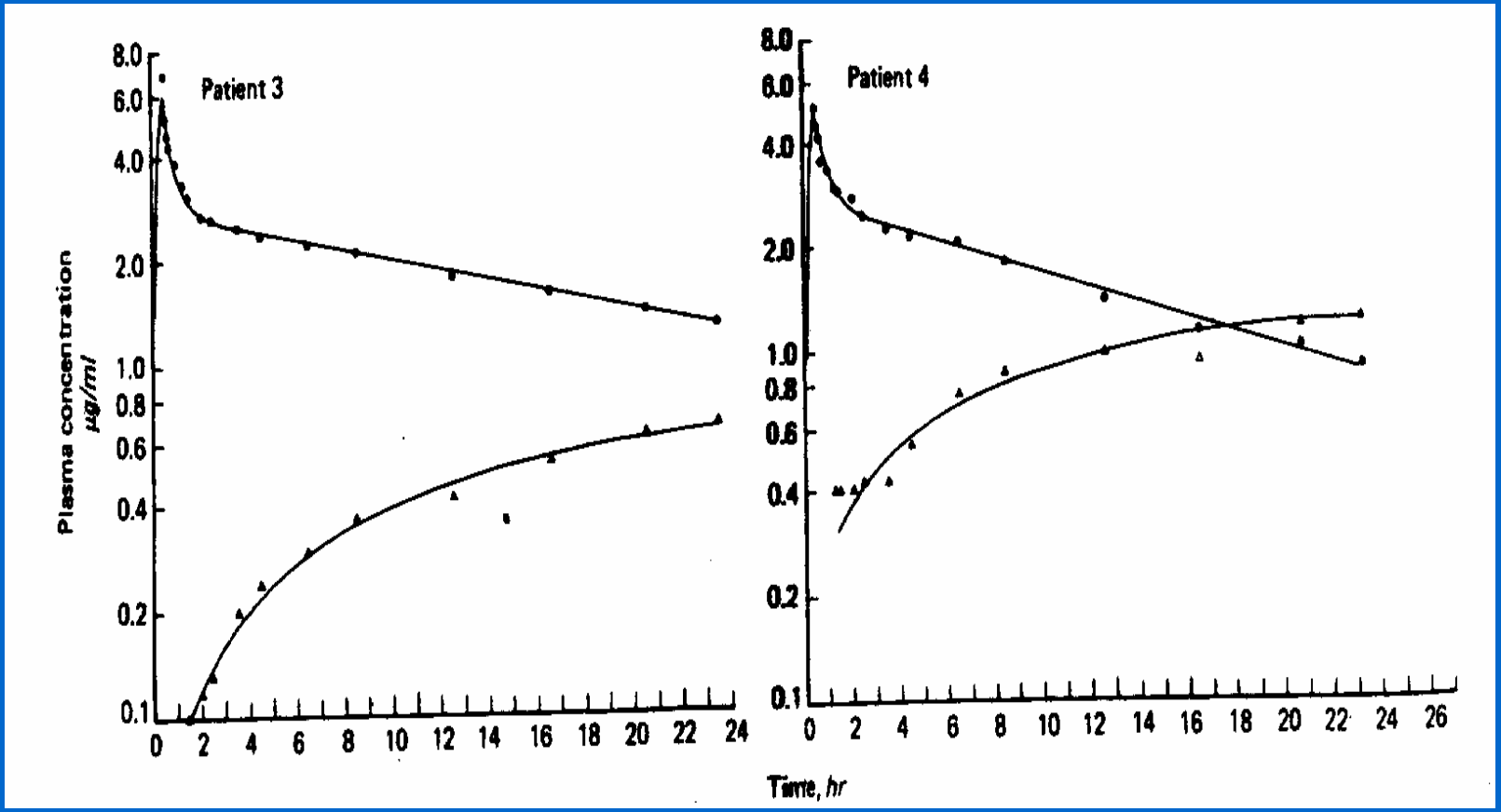


PROCAINAMIDE KINETICS IN NORMAL SUBJECTS *



* From: Gibson TP. Kidney Int 1977;12:422-9.

PROCAINAMIDE KINETICS IN DIALYSIS PATIENTS*



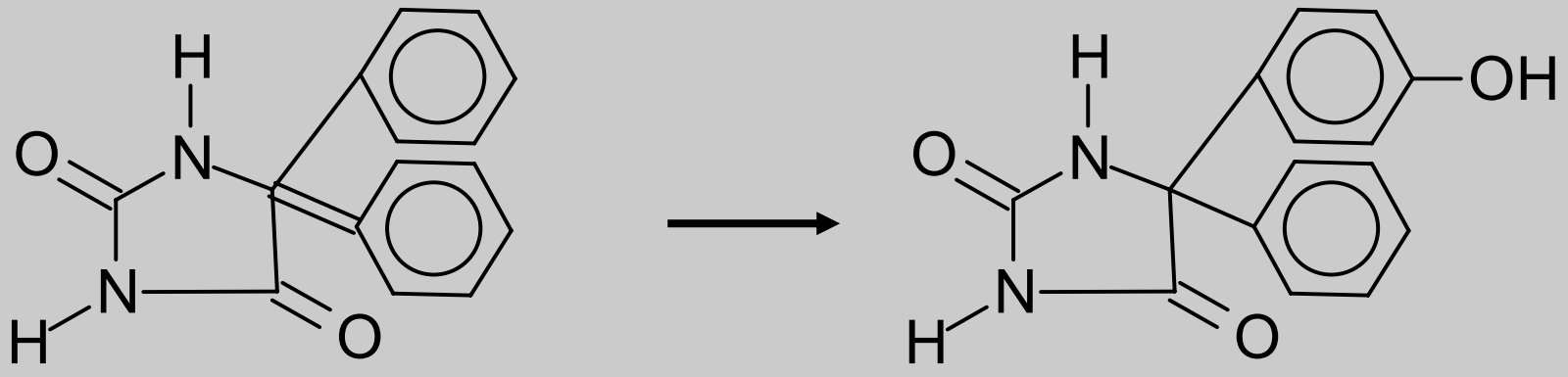
* From: Gibson TP. Kidney Int 1977;12:422-9.

PROCAINAMIDE KINETICS IN DIALYSIS PATIENTS*

	NORMALS		UREMIC PATIENTS	
	FAST	SLOW	FAST	SLOW
$V_{d(ss)}$ (L/kg)	1.95	1.93	1.41	1.93
$T_{1/2}$ (hr)	2.6	3.5	12.2	17.0
CL_E (L/kg)	809	600	118	94
CL_R (L/kg)	426	357	0	0
CL_{NR} (L/kg)	383	243	118	94

* From: Gibson TP. Kidney Int 1977;12:422-9.

PHENYTOIN HYDROXYLATION



PHENYTOIN ***p*** **- HPPH**

PHENYTOIN KINETICS IN DIALYSIS PATIENTS*

	NORMALS	UREMIC PATIENTS
% UNBOUND (f)	12%	26%
$V_{d(AREA)}$	0.64 L/kg	1.40 L/kg
CL_H	2.46 L/hr	7.63 L/hr
CL_{int}	20.3 L/hr	29.9 L/hr

* From: Odar-Cederlöf I, Borgå O: Eur J Clin Pharmacol 1974;7:31-7.

RESTRICTIVE VS. NONRESTRICTIVE ELIMINATION

RESTRICTIVE:

CLEARANCE DEPENDS ON PROTEIN BINDING ($CL = f_U \bullet CL_{int}$)

NONRESTRICTIVE:

CLEARANCE INDEPENDENT OF PROTEIN BINDING ($CL = Q$)

EFFECT OF BINDING CHANGES ON APPARENT DISTRIBUTION VOLUME*

$$V_d = ECF + \varphi f_u (TBW - ECF)$$

* Atkinson AJ Jr, et al. Tremds Pharmacol Sci 1991;12:96-101.

GOALS OF RENAL DISEASE EFFECTS LECTURE

- **EFFECT OF RENAL DISEASE ON DRUG DISTRIBTION**

  - **PLASMA PROTEIN BINDING**

    EXAMPLE: PHENYTOIN

  - **TISSUE BINDING**

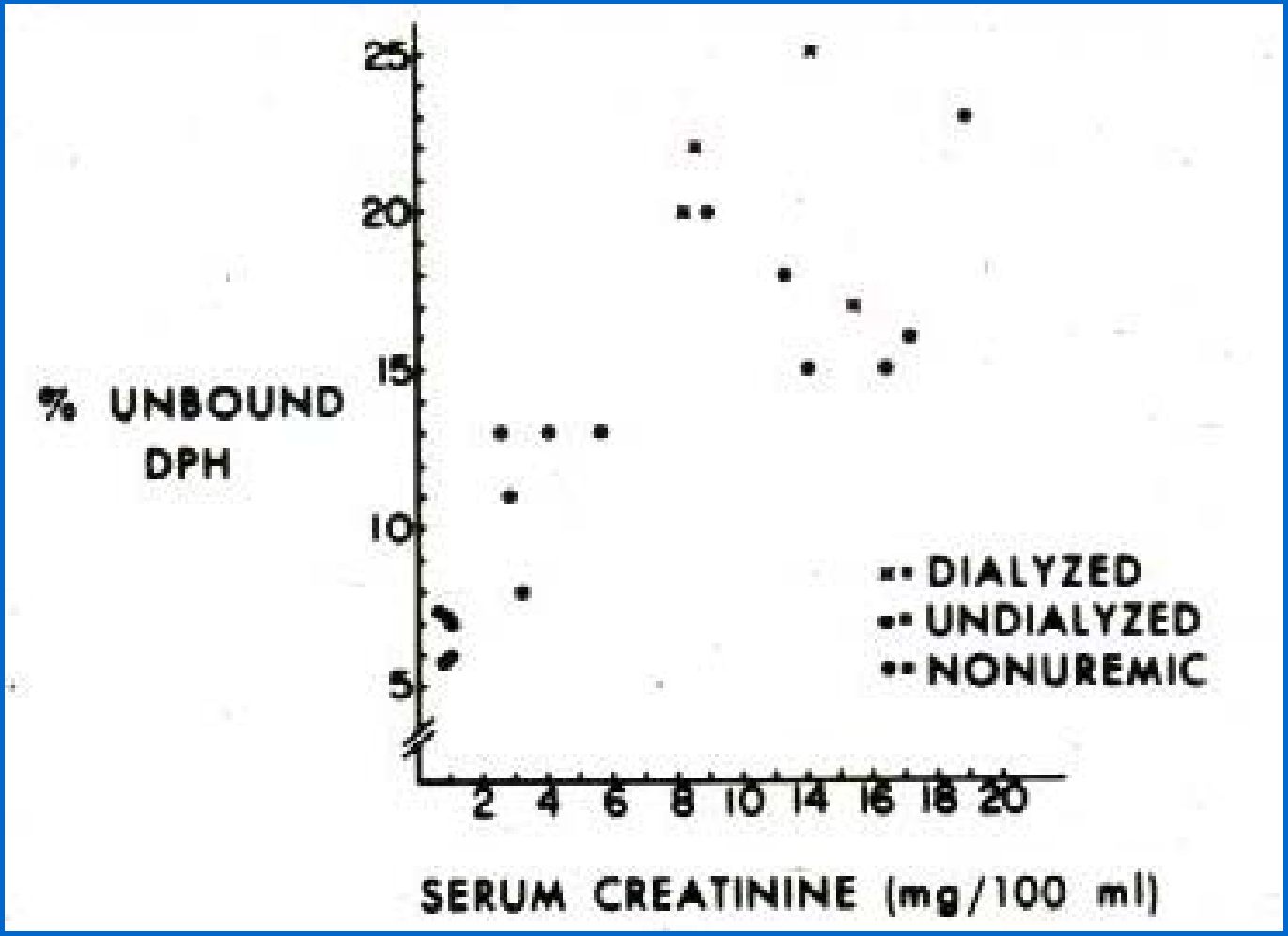
    EXAMPLE: DIGOXIN

EFFECT OF RENAL DISEASE ON BINDING TO PLASMA PROTEINS*

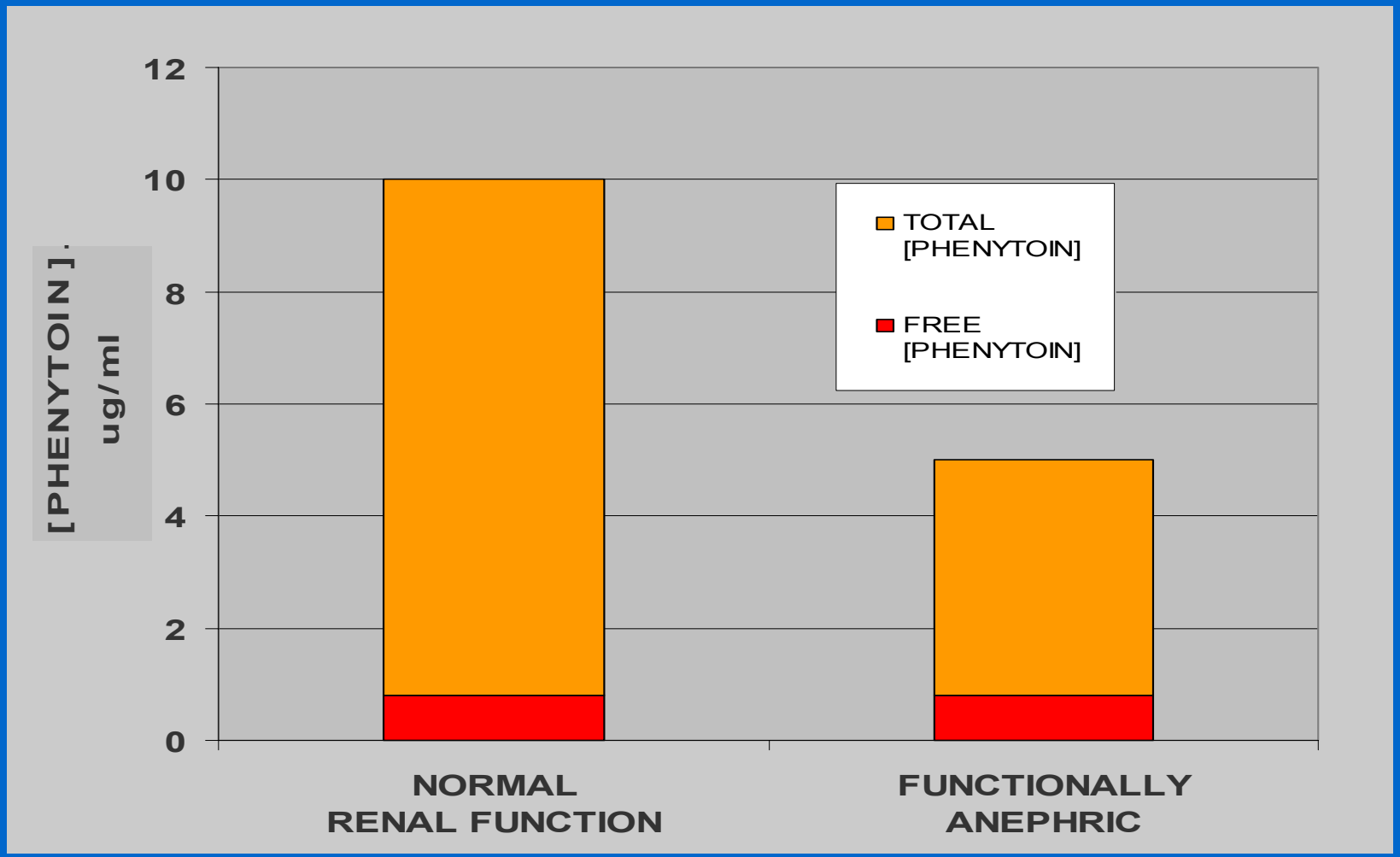
BASIC OR NEUTRAL DRUGS:	NORMAL OR SLIGHTLY REDUCED
ACIDIC DRUGS:	REDUCED FOR MOST

* From: Reidenberg MM, Drayer DE: Clin Pharmacokinet 1984;9(Suppl. 1):18-26.

EFFECT OF RENAL DISEASE ON PHENYTOIN PROTEIN BINDING



FREE AND TOTAL PHENYTOIN LEVELS



THERAPEUTIC RANGE OF PHENYTOIN LEVELS IN DIALYSIS PATIENTS

BASED ON TOTAL LEVELS: **5 - 10 μg/mL**

BASED ON "FREE" LEVELS: **0.8 - 1.6 μg/mL**

PRIMARY DIFFICULTIES IN PHENYTOIN DOSE ADJUSTMENT

- NONLINEAR ELIMINATION KINETICS
- VARIATION IN BINDING TO PLASMA PROTEINS

NONCANCER DRUGS CAUSING ADR'S*

PHENYTOIN**	CARBAMAZEPINE**
PREDNISONE	CODEINE
DIGOXIN**	LITHIUM**
AMIODARONE	THEOPHYLLINE**
ASPIRIN**	DESIPRAMINE**
CO-TRIMOXAZOLE	DEXAMETHASONE
PENTAMIDINE	GENTAMICIN**

* 1988 NMH DATA (CLIN PHARMACOL THER 1996;60:363-7)

** DRUGS FOR WHICH PLASMA LEVELS ARE AVAILABLE

IMPAIRED RENAL FUNCTION REDUCES DIGOXIN DISTRIBUTION VOLUME*

$$V_d = 3.84 \bullet wt(kg) + 3.12\ CL_{CR}(ml/min)$$

* Sheiner LB, et al. J Pharmacokinet Biopharm 1977;5:445-79.

EFFECT OF RENAL DISEASE ON BIOAVAILABILITY

UNCHANGED BIOAVAILABILITY:

CIMETIDINE

DIGOXIN

DECREASED BIOAVAILABILITY:

D-XYLOSE

FUROSEMIDE

INCREASED BIOAVAILABILITY:

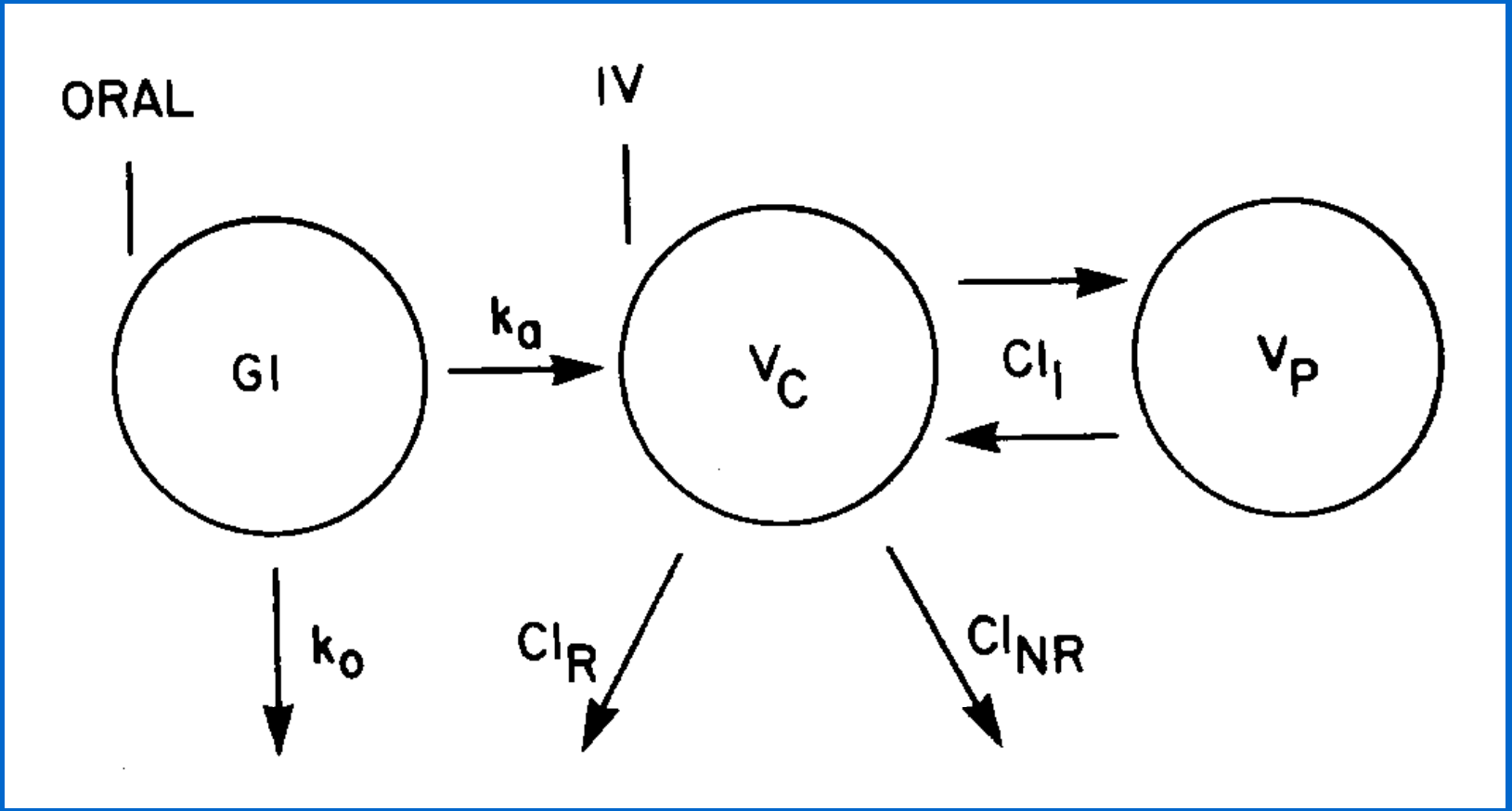
PROPRANOLOL

DEXTROPROPOXYPHENE

CRITERIA FOR NORMAL D-XYLOSE ABSORPTION

5-hr URINE RECOVERY	> 4 g
[SERUM] 1 hr AFTER DOSE	≥ 0.2 mg/mL
% DOSE ABSORBED	> 42%
k_a	> 0.37 hr^{-1}

KINETIC MODEL USED TO ANALYZE D-XYLOSE ABSORPTION*

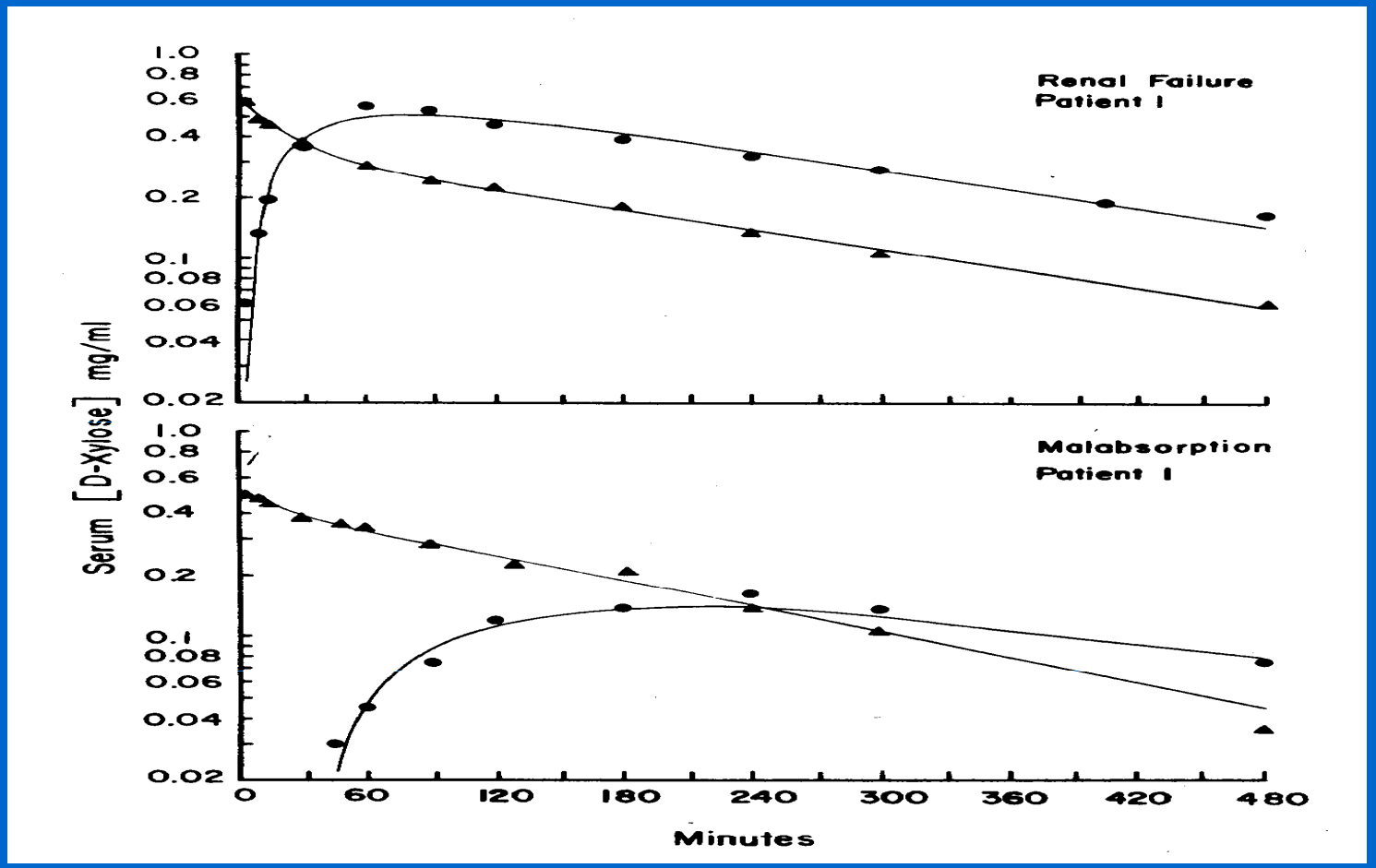


* From Worwag EM, et al. Clin Pharmacol Ther 1987;41:351-7.

CALCULATION OF BIOAVAILABILITY FROM FIRST-ORDER ABSORPTION MODEL

$$F = \frac{k_a}{k_a + k_o}$$

D-XYLOSE ABSORPTION WITH MODERATE RENAL IMPAIRMENT*



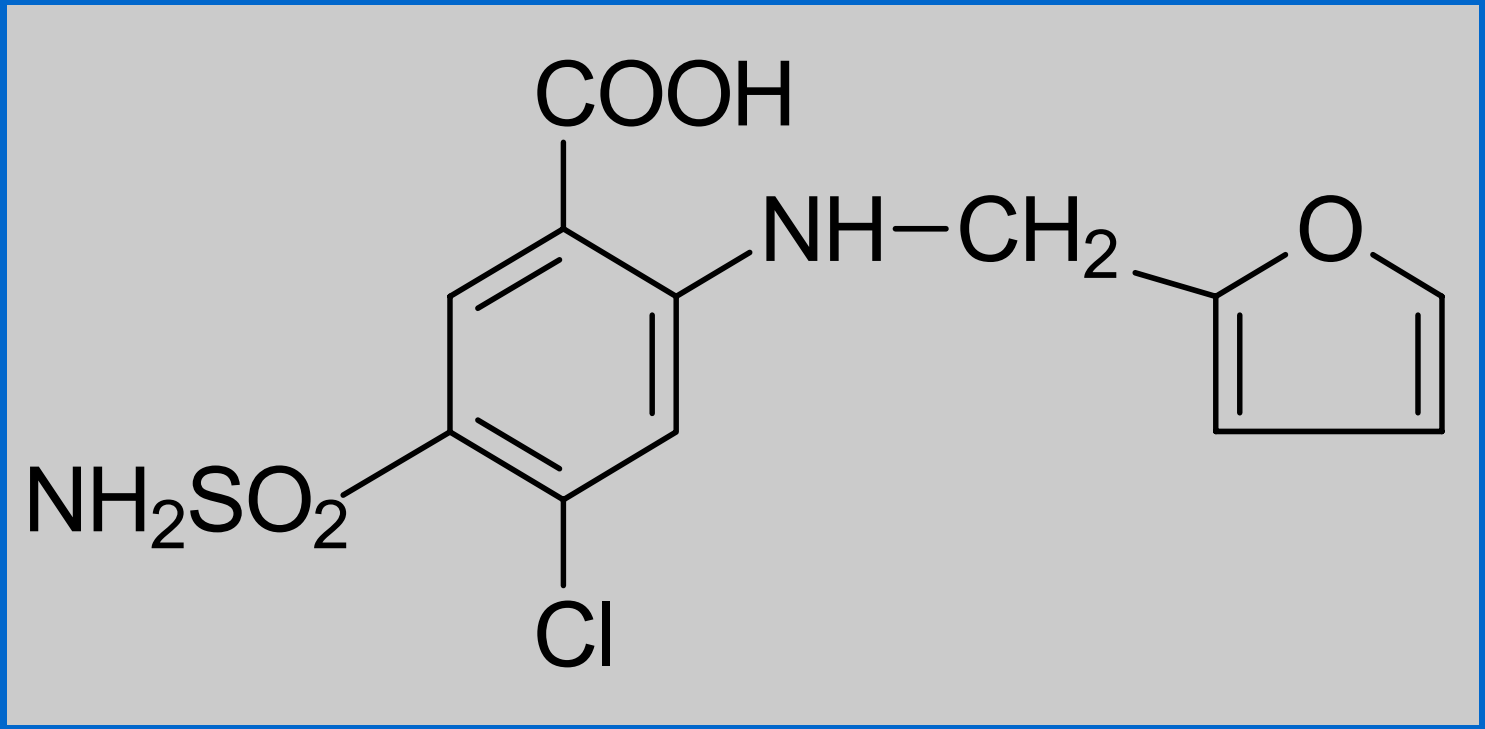
* From Worwag EM, et al. Clin Pharmacol Ther 1987;41:351-7.

EFFECT OF RENAL DISEASE ON D-XYLOSE ABSORPTION*

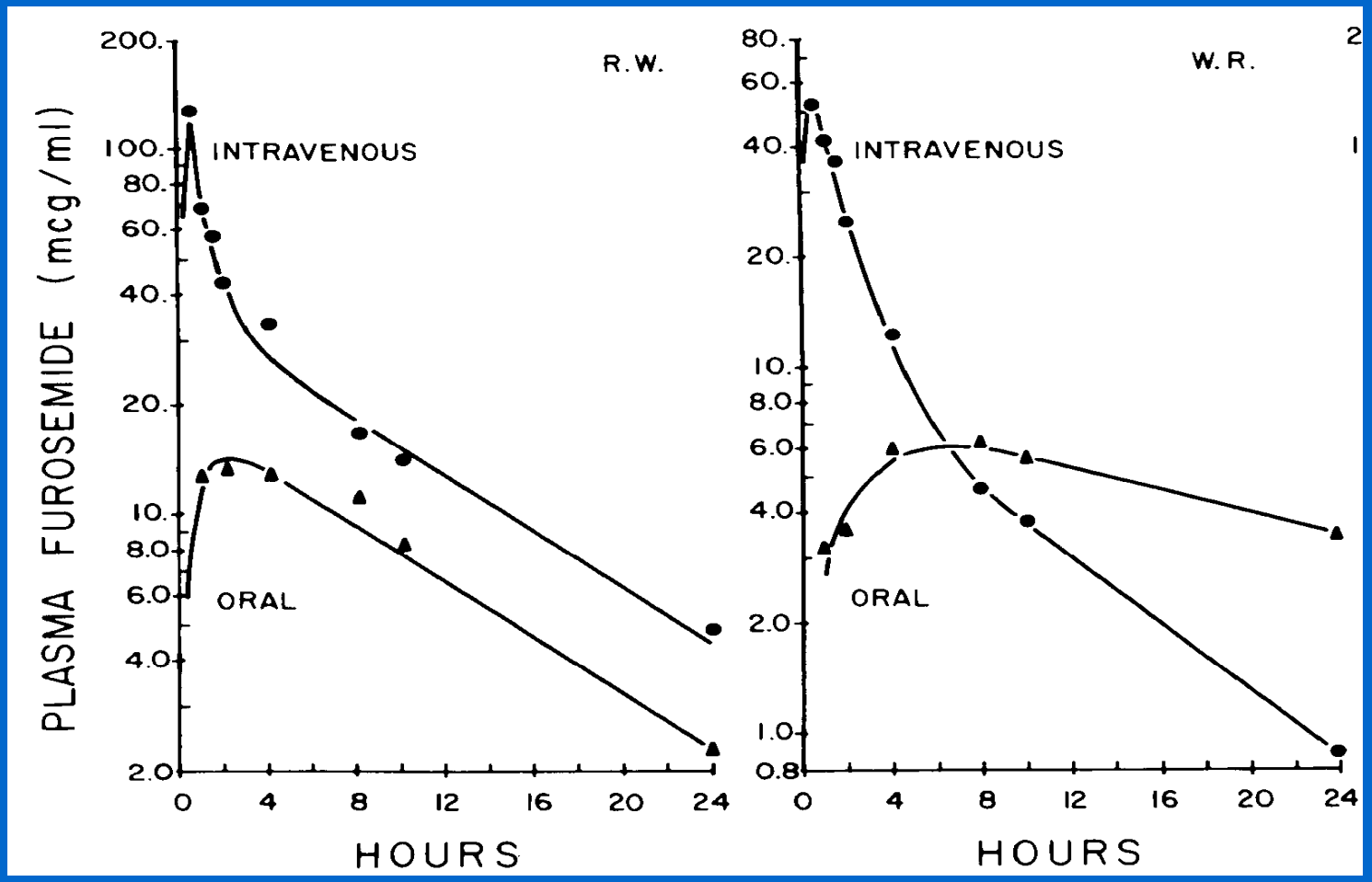
PATIENT GROUP	k_a (hr^{-1})	k_o (hr^{-1})	% DOSE ABSORBED
NORMALS	1.03 ± 0.33	0.49 ± 0.35	69.4 ± 13.6
MODERATE	0.64 ± 0.28	0.19 ± 0.15	77.4 ± 14.8
DIALYSIS	0.56 ± 0.42	0.67 ± 0.61	48.6 ± 13.3

* From: Worwag EM et al. Clin Pharmacol Ther 1987;41:351-7.

FUROSEMIDE

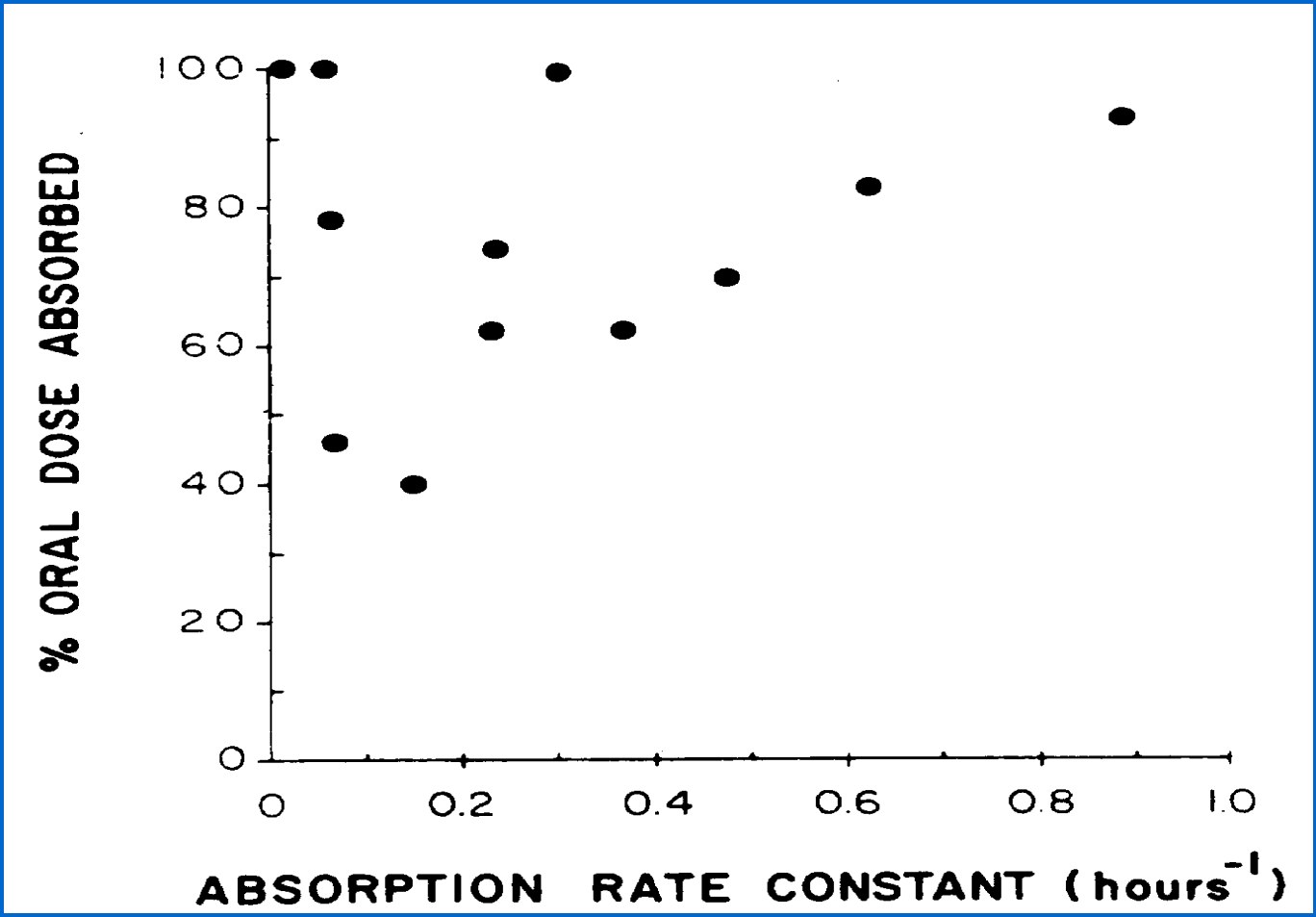


FUROSEMIDE ABSORPTION WITH ADVANCED RENAL IMPAIRMENT*



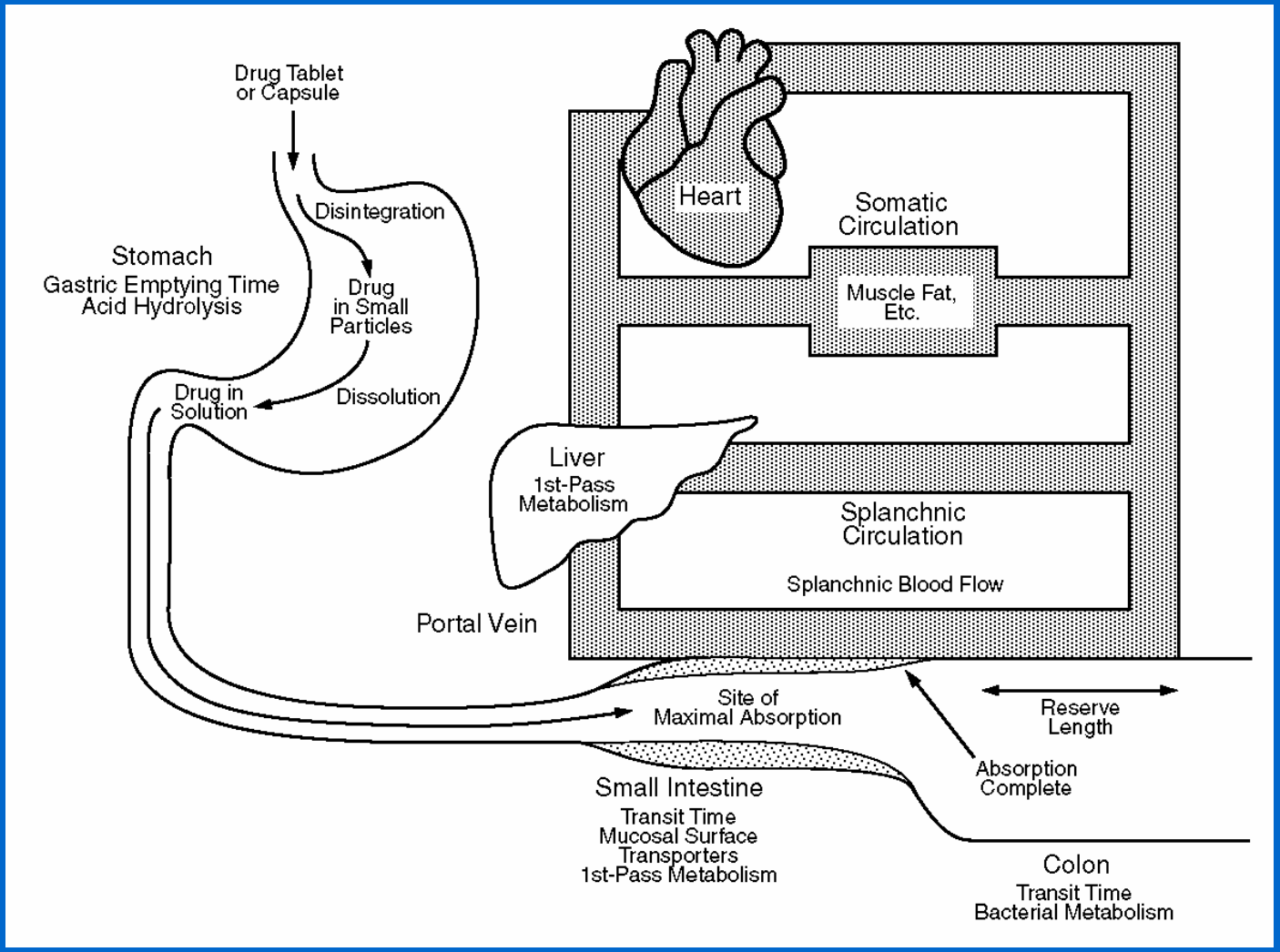
* From Huang CM, et al. Clin Pharmacol Ther 1974;16:659-66.

RELATIONSHIP BETWEEN FUROSEMIDE k_a AND F*

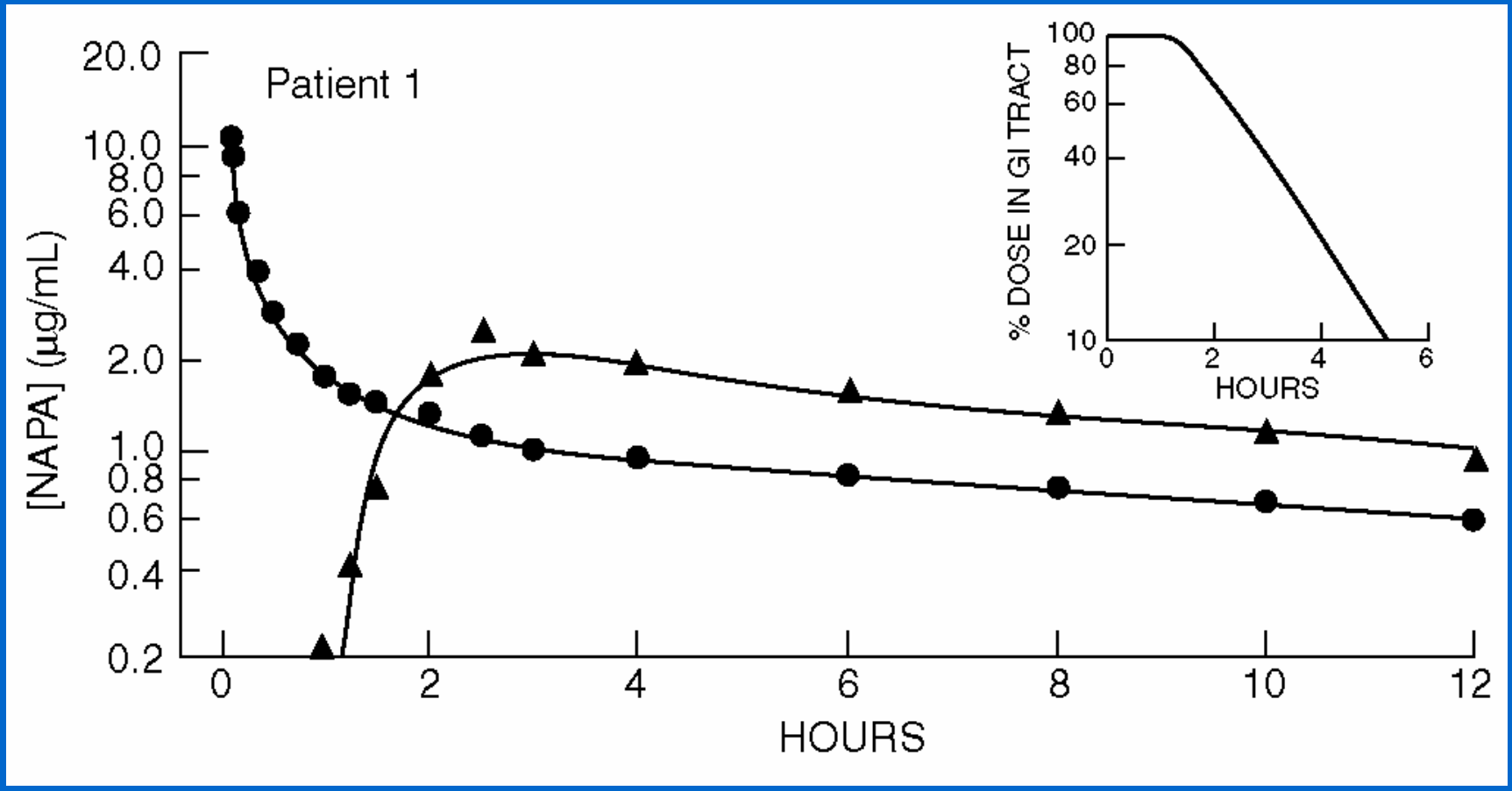


* From Huang CM, et al. Clin Pharmacol Ther 1974;16:659-66.

FACTORS AFFECTING RATE AND EXTENT OF DRUG ABSORPTION



SIMULTANEOUS ADMINISTRATION OF ORAL NAPA AND IV NAPA-C^{13}*



* From Atkinson AJ Jr, et al. Clin Pharmacol Ther 1989;46:182-9.