Effects of Renal Disease on Pharmacokinetics

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GOALS of Effects of Renal Disease on Pharmacokinetics Lecture

Dose Adjustment in Patients with Renal Impairment

Effect of Renal Disease on:

- **Renal Drug Elimination**
- **Hepatic Drug Metabolism**
- **Drug Distribution**
- **Drug Absorption**

GOALS Of Effects of Renal Disease on PK Lecture

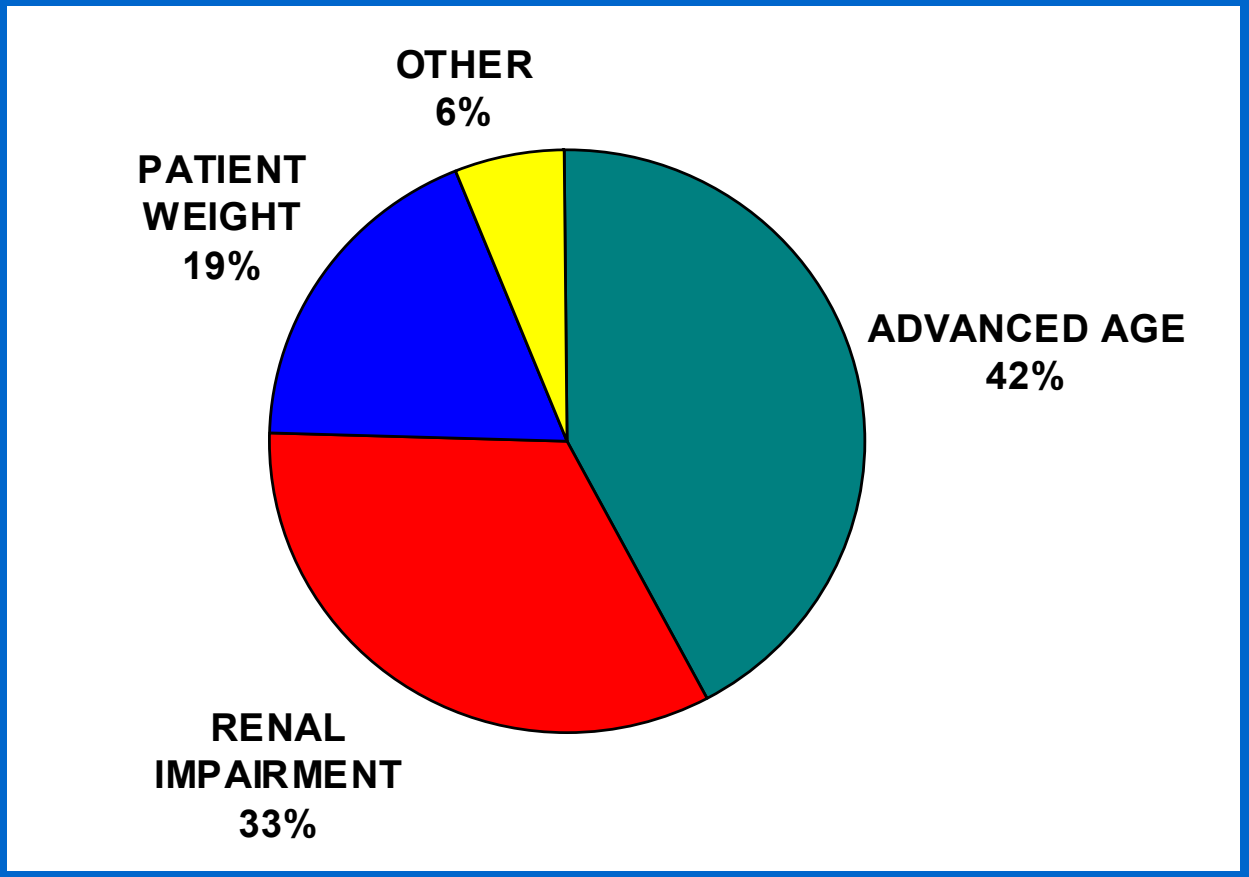
* ***DOSE ADJUSTMENT*** **in Patients with Renal Impairment**

  Statement of the Problem

  How is renal function assessed?

  How is drug dose adjusted based on this assessment?

PATHOPHYSIOLOGIC FACTORS
NOT ACCOUNTED FOR IN DRUG DOSING*



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

Central Role of *DRUG LABEL*

The *DRUG LABEL* is the primary source of drug prescribing information and is *reviewed by the FDA* as part of the drug approval process.

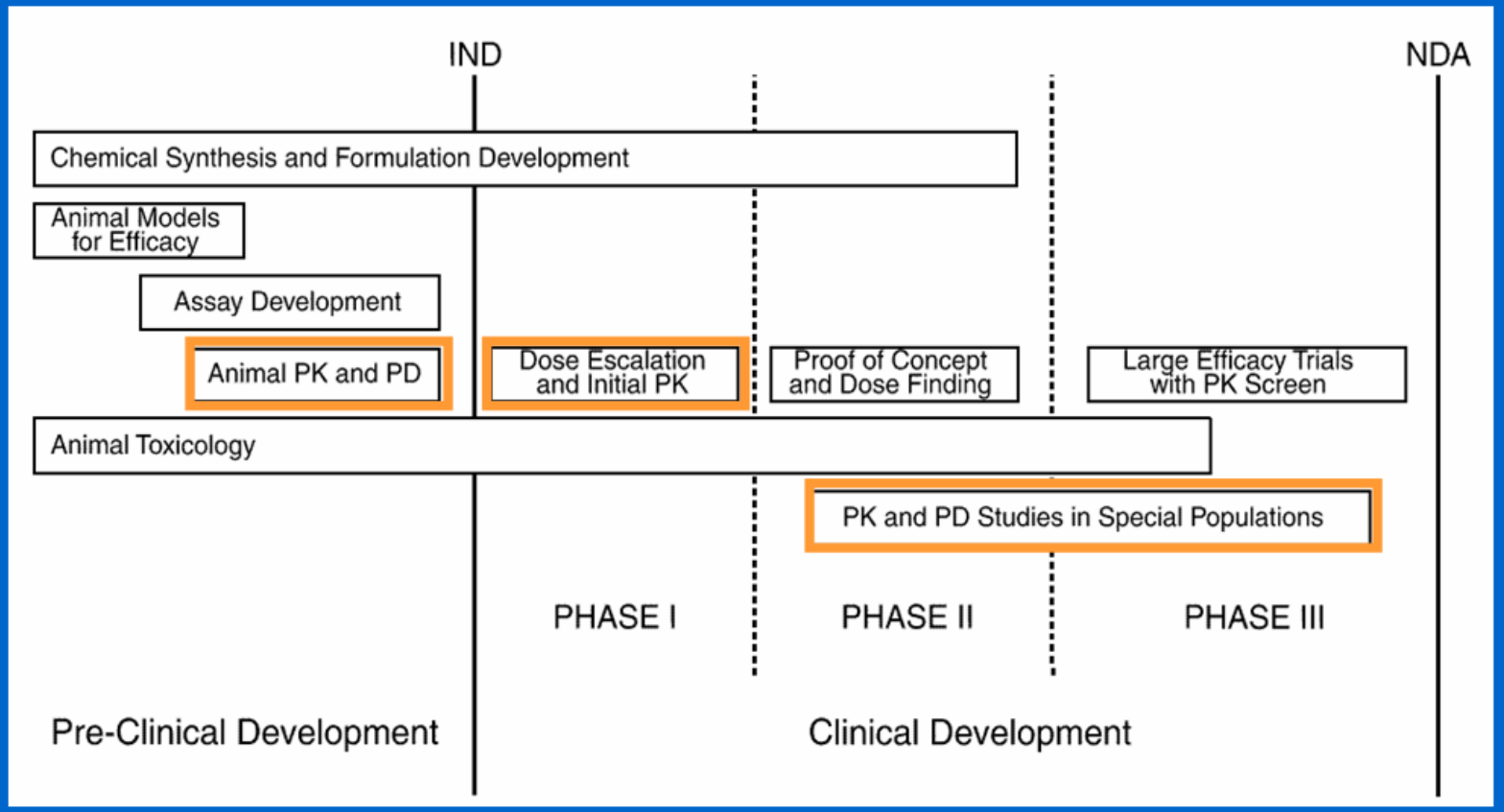
As such the drug label is *a distillate of the entire drug development process.*

INFORMATION CONTENT
OF CURRENT DRUG LABELS*

CORE INFORMATION CATEGORY	Inclusion of Desirable Data Elements MEAN (95% CI)	
MECHANISM OF ACTION	88%	(84% - 93%)
PHARMACODYNAMICS	43%	(37% - 49%)
DRUG METABOLISM	23%	(16% - 29%)
PHARMACOKINETICS	42%	(35% - 49%)
DOSE ADJUSTMENT	37%	(32% - 42%)

* Spyker DA, et al. Clin Pharmacol Ther 2000;67:196-200.

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

GOALS of Renal Disease Effects Lecture

* ***DOSE ADJUSTMENT*** **in Patients with Renal Impairment**

  - **Statement of the Problem**

  - **How is renal function assessed?**

  - **How is drug dose adjusted based on this assessment?**

ELIMINATION by Different Routes

MEASUREMENTS	RENAL	HEPATIC	DIALYSIS
Blood Flow	+*	+*	+
Afferent Concentration	+	+	+
Efferent Concentration	0	0	+
Eliminated Drug	+	0	+

**not actually measured in routine PK studies*

RENAL CLEARANCE EQUATION

$$CL = \frac{U \times V}{P}$$

U = URINE CONCENTRATION

V = URINE VOLUME

P = PLASMA CONCENTRATION

CLEARANCE TECHNIQUES FOR ASSESSING RENAL FUNCTION

GLOMERULAR FILTRATION:

Normal: 120 – 130 mL/min/1.73 m^2

***CLEARANCE MARKERS*:**

Inulin

Creatinine

^{125}I-Iothalamate

RENAL BLOOD FLOW:

Normal: ♂ 1,209 ± 256 mL/min/1.73 m^2

♀ 982 ± 184 mL/min/1.73 m^2

***CLEARANCE MARKER*:**

Para-Aminohippuric Acid

GOALS of Renal Disease Effects Lecture

* ***DOSE ADJUSTMENT*** **in Patients with Renal Impairment**

  - **How is renal function assessed?**
    (***Usually estimated from the Cockcroft and Gault Equation if renal function is stable)***

STEADY STATE CONCENTRATION

Continuous Infusion:

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

Intermittent Dosing:

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

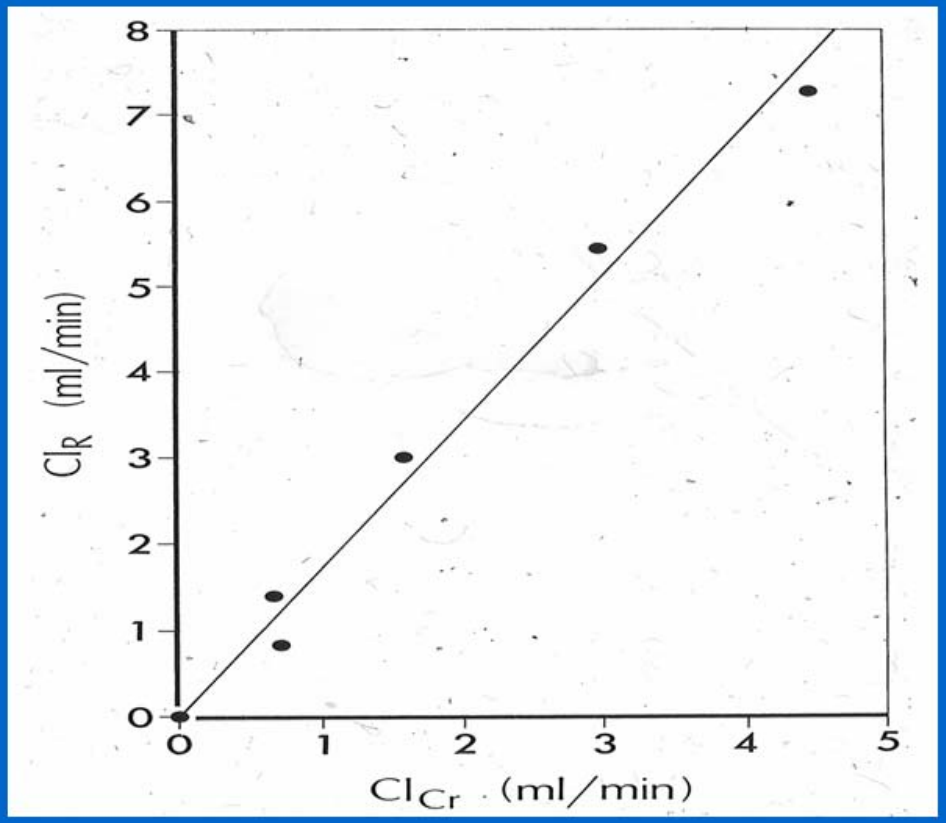
ADDITIVITY OF CLEARANCES

$$CL_E = CL_R + CL_{NR}$$

CL_R = RENAL CLEARANCE

CL_{NR} = NON-RENAL CLEARANCE

CL_R VS. CL_{Cr} IS LINEAR*



$CL_R = \alpha\ CL_{Cr}$

$CL_R > CL_{Cr}$

IMPLIES NET TUBULAR SECRETION

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

DETTLI Approach*

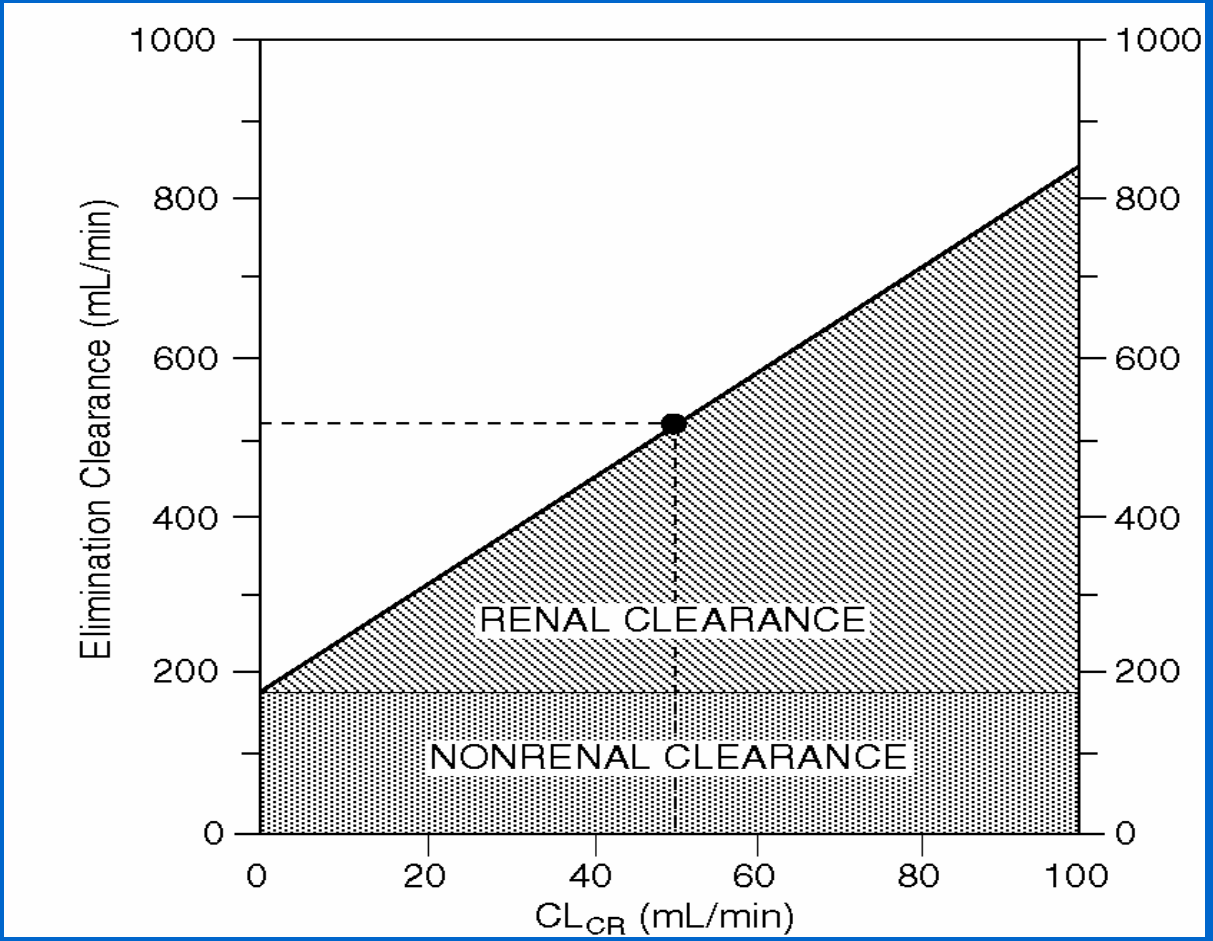
$$CL_R = \alpha CL_{Cr}$$

$$CL_E = CL_R + CL_{NR}$$

NEED: 1. CL_E IN NORMAL SUBJECTS
2. NORMAL % RENAL EXCRETION

* Dettli L. Med Clin North Am 1974;58:977-85

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}
  - *Intact Nephron* Hypothesis
  - Some drugs ↓ *SECRETION* > *GFR* with aging*

* Reidenberg MM, et al. Clin Pharmacol Ther 1980;28:732-5.

CIMETIDINE Case History

A 67-year-old veteran had been functionally anephric, requiring outpatient hemodialysis for several years. He was hospitalized for revision of his arteriovenous shunt and postoperatively complained of symptoms of gastroesophageal reflux. This complaint prompted institution of cimetidine therapy in a dose of 300 mg every 6 hours.

CIMETIDINE Case History (cont.)

<u>*Rationale* for Prescribed Cimetidine Dose</u>:

At that time*, 600 mg every 6 hours was the usual cimetidine dose for patients with normal renal function and the *Physician's Desk Reference* recommended *halving the cimetidine dose for patients "with creatinine clearance less than 30 cc/min".

CIMETIDINE Case History (cont.)

Three days later the patient was noted to be confused. The nephrology service entertained the diagnosis of *dialysis dementia* and informed the family that hemodialysis might be discontinued. The teaching attending suggested that *cimetidine be discontinued first.* Two days later the patient was alert and was discharged from the hospital to resume outpatient hemodialysis therapy.

LABELING FOR CIMETIDINE*

* ***DOSAGE ADJUSTMENT***

  1/2 normal dose if CL_{Cr} < 30 mL/min

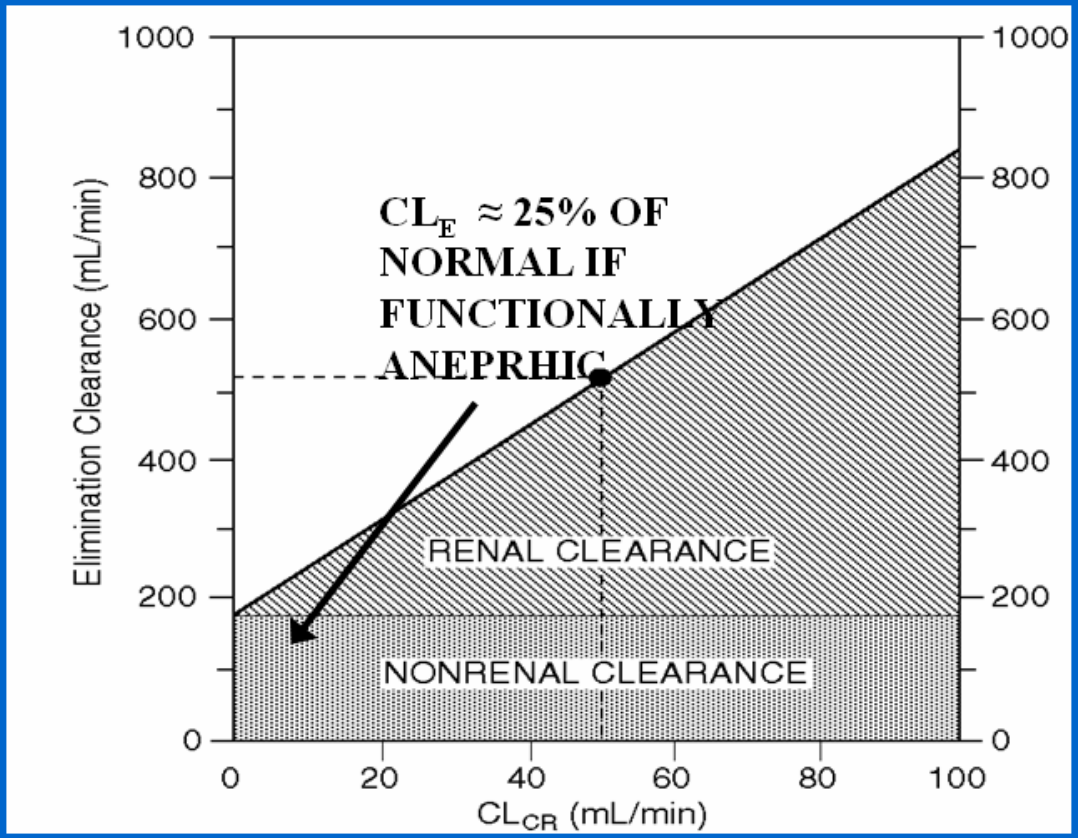
* **PHARMACOKINETICS**

  Following I.V. of I.M. administration in *normal subjects*,

  - 75% of drug is recovered from the urine as *parent compound*.

*** Physician's Desk Reference. 58th edition, 2004.**

NOMOGRAM FOR CIMETIDINE DOSING*



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

DOSE ADJUSTMENT OPTIONS FOR PATIENTS WITH RENAL IMPAIRMENT

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

* MAINTAIN USUAL DOSING INTERVAL BUT *REDUCE DOSE* IN PROPORTION TO $\downarrow CL_E$
* MAINTAIN USUAL DOSE BUT *INCREASE DOSING INTERVAL* IN PROPORTION TO $\downarrow CL_E$
* *ADJUST BOTH* DOSE AND DOSING INTERVAL

ELIMINATION HALF-LIFE

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

GOALS of Renal Disease Effects Lecture

* **EFFECT OF RENAL DISEASE ON RENAL DRUG ELIMINATION**

  - ***MECHANISMS*** **OF RENAL DRUG ELIMINATION**

  - **CONCEPT OF** ***RESTRICTIVE VS. NONRESTRICTIVE*** **ELIMINATION**

MECHANISMS of Renal Drug Elimination

Glomerular Filtration

Renal Tubular Secretion

Reabsorption by Non-Ionic Diffusion

Active Reabsorption

MECHANISMS OF RENAL ELIMINATION

GLOMERULAR FILTRATION

* Affects all drugs and metabolites of **appropriate molecular size.**
* *Influenced* by **protein binding**

Drug Filtration Rate = GFR x f_u x [Drug]
(f_u = free fraction)

RENAL TUBULAR SECRETION

* *Not influenced* by protein binding
* May be affected by *other drugs*, etc.

EXAMPLES:

Active Drugs:	ACIDS – Penicillin
	BASES – Procainamide
Metabolites:	Glucuronides, Hippurates, etc.

RESTRICTIVE vs. *NONRESTRICTIVE* ELIMINATION

RESTRICTIVE:

Clearance *DEPENDS* on Protein Binding.

KIDNEY: Drug Filtration Rate = f_U • GFR
LIVER: CL = f_U • Cl_{int}

NONRESTRICTIVE:

Clearance *INDEPENDENT* of Protein Binding

KIDNEY: CL = Q (renal blood flow)

***EXAMPLE*: PARA-AMINOHIPPURATE CLEARANCE MEASURES RENAL BLOOD FLOW.**

INTRINSIC CLEARANCE

INTRINSIC CLEARANCE **IS THE ELIMINATION CLEARANCE THAT *WOULD BE OBSERVED* IN THE *ABSENCE OF ANY PROTEIN BINDING RESTRICTIONS*.**

RESTRICTIVE vs. *NONRESTRICTIVE* ELIMINATION

RESTRICTIVE:

Clearance *DEPENDS* on Protein Binding

KIDNEY: Drug Filtration Rate = f_U • GFR
LIVER: CL = f_U • Cl_{int}

NONRESTRICTIVE:

Clearance *INDEPENDENT* of Protein Binding

KIDNEY: CL = Q (renal blood flow)

LIVER: CL = Q (hepatic blood flow)

Renal *REABSORPTION* Mechanisms

REABSORPTION BY NON-IONIC DIFFUSION

* **Affects weak acids and weak bases.**
* **Only important if excretion of *free drug* is major elimination pathway.**

  ***EXAMPLES*:**

  Weak Acids: PHENOBARBITAL
  Weak Bases: QUINIDINE

ACTIVE REABSORPTION

* **Affects ions, not proved for other drugs.**

  ***EXAMPLES*:**

  Halides: FLUORIDE, BROMIDE
  Alkaline Metals: LITHIUM

RENAL EXCRETION OF DRUGS

INTACT NEPHRON HYPOTHESIS: Provides a basis for dose adjustment when renal excretion of drug is impaired.

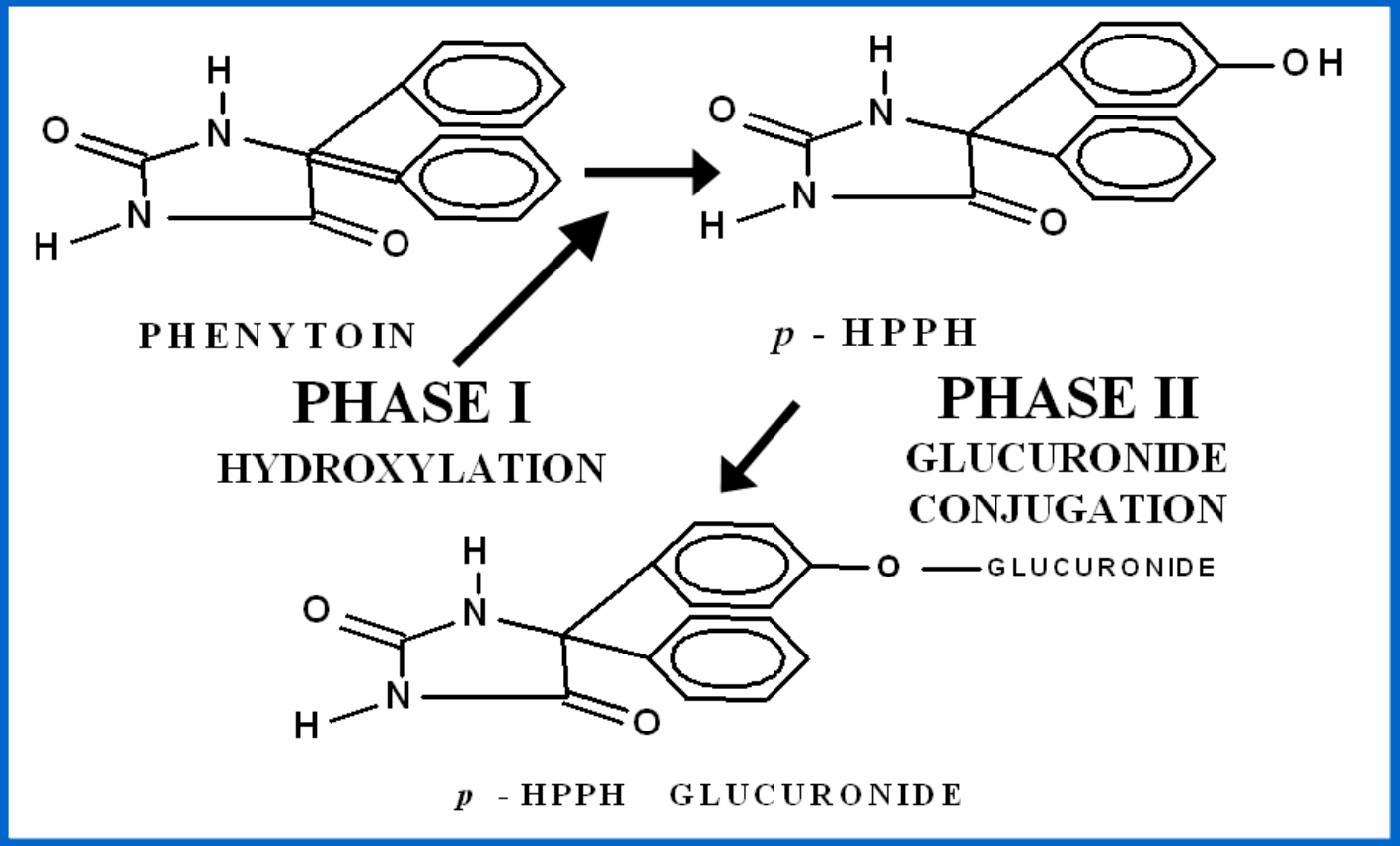
* **Regardless of mechanism, *renal drug elimination declines in parallel with decreases in GFR.***
* **Therefore, CL_{Cr} can be used to assess impact of renal impairment on renal excretion of drugs.**

WHAT ABOUT OTHER EXCRETION ROUTES?

GOALS of Renal Disease Effects Lecture

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

PHASE I AND PHASE II METABOLIC REACTIONS



Effect of Renal Disease on *PHASE I* DRUG METABOLISM

OXIDATIONS — *Normal or Increased*

Example: **Phenytoin**

REDUCTIONS — *Slowed*

Example: **Hydrocortisone**

Effect of Renal Disease on *PHASE I* DRUG METABOLISM

HYDROLYSIS

Plasma esterase — ***Slowed***

Example: **Procaine**

Plasma peptidase — ***Normal***

Example: **Angiotensin**

Tissue peptidase — ***Slowed***

Example: **Insulin**

Effect of Renal Disease on *PHASE II* DRUG METABOLISM

GLUCURONIDATION — ***Normal***

Example: **Hydrocortisone**

ACETYLATION — ***Slowed***

Example: **Procainamide**

GLYCINE CONJUGATION — ***Slowed***

Example: ***p*-Aminosalicylic acid**

Effect of Renal Disease on *PHASE II* DRUG METABOLISM

O-METHYLATION ***Normal***

Example: **Methyldopa**

SULFATE CONJUGATION ***Normal***

Example: **Acetaminophen**

GOALS of Renal Disease Effects Lecture

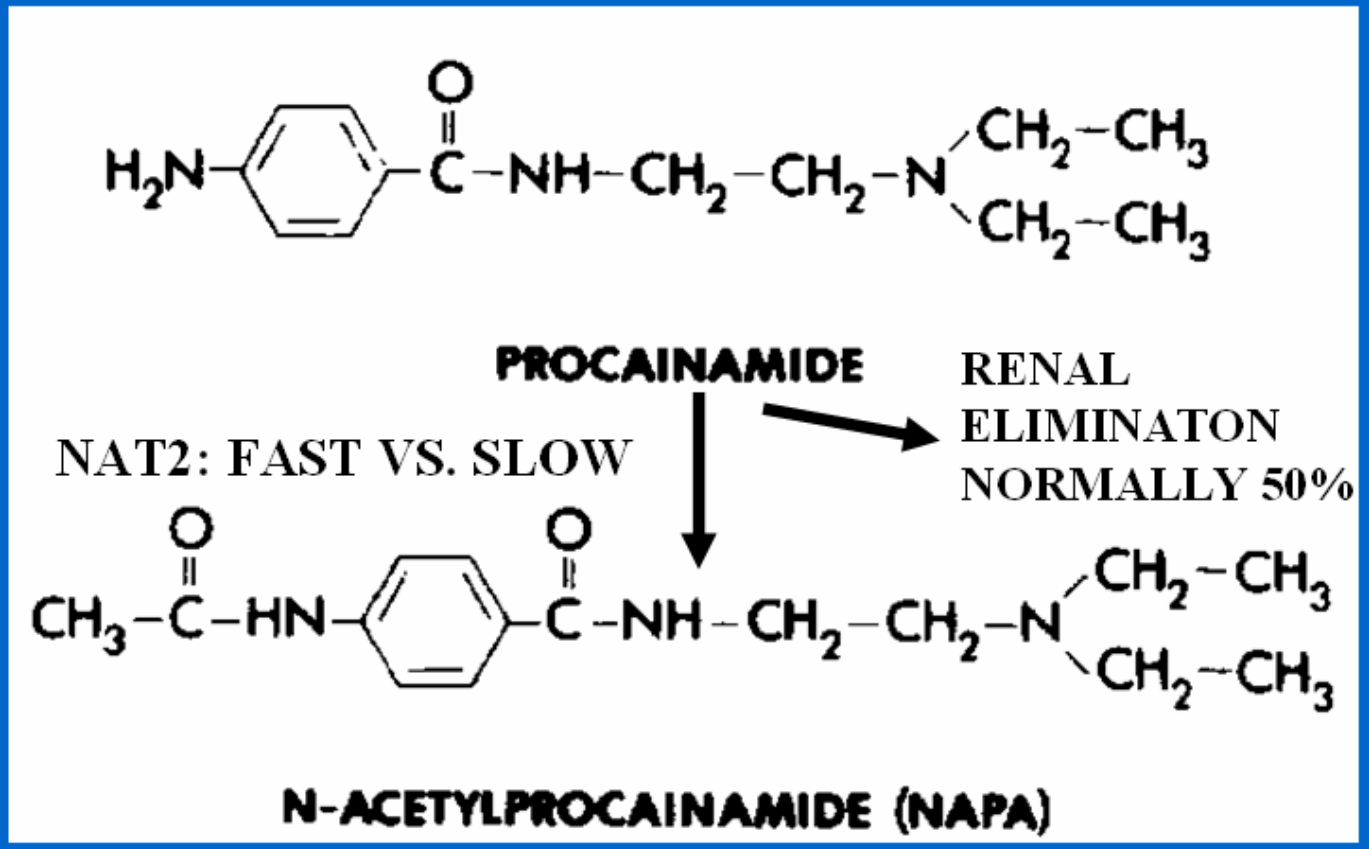
* **EFFECT OF RENAL DISEASE ON *DRUG METABOLISM***

* ***EXAMPLES:***

PROCAINAMIDE - Acetylation

PHENYTOIN - Hydroxylation

PROCAINAMIDE *ACETYLATION*

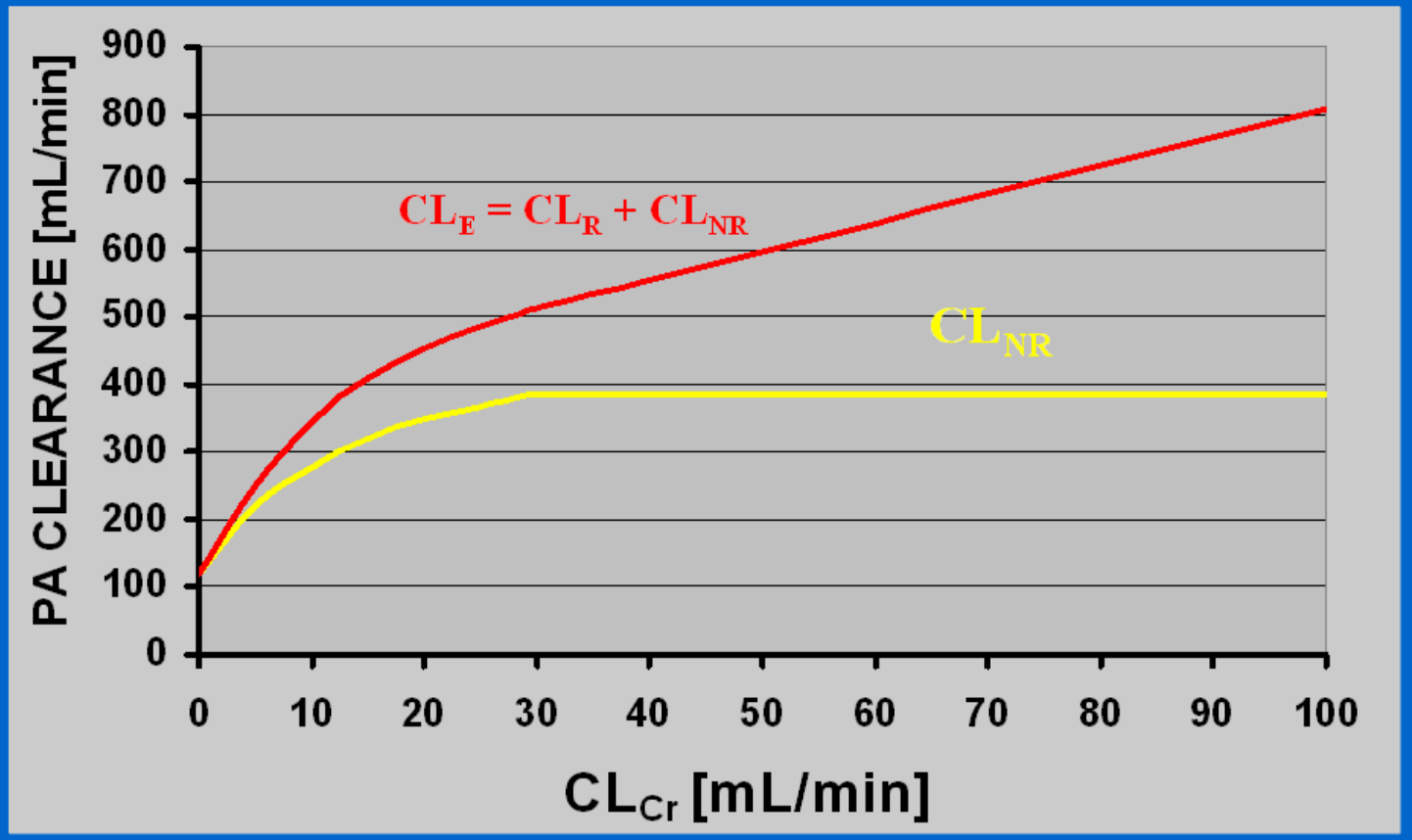


Procainamide Kinetics in *DIALYSIS PATIENTS**

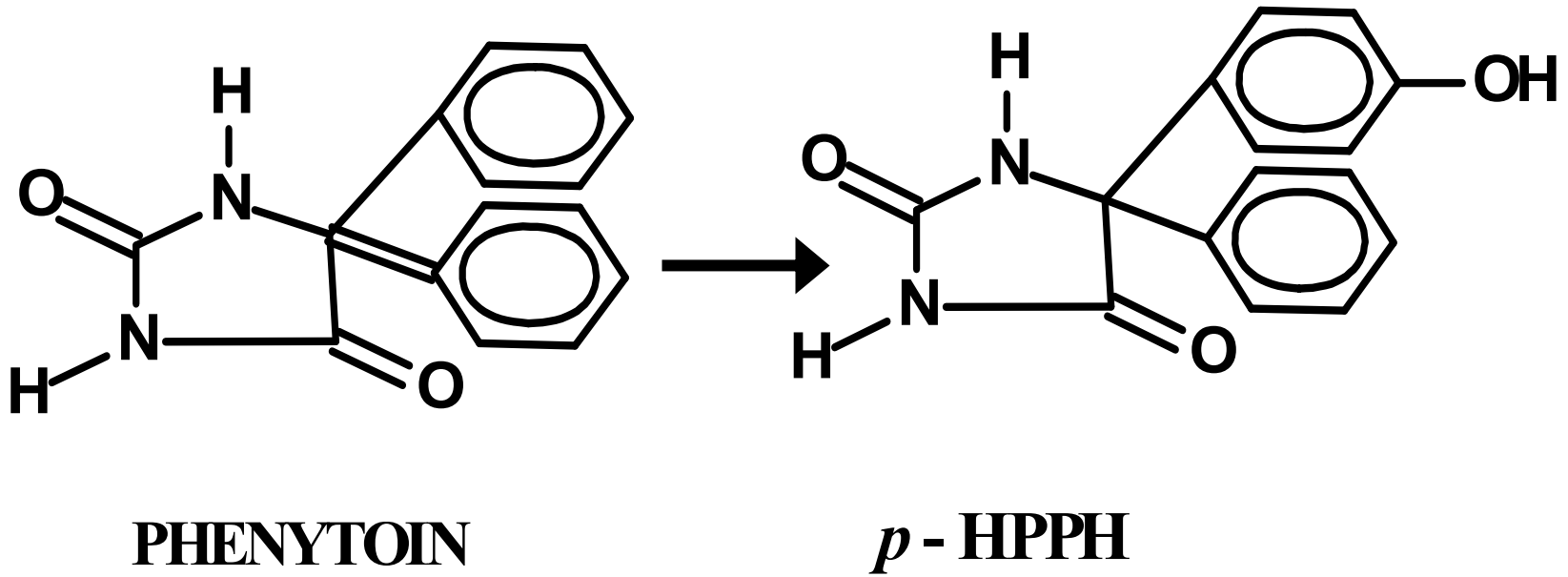
	NORMALS		*FUNCTIONALLY ANEPHRIC PATIENTS*	
	Fast	Slow	Fast	Slow
$T_{1/2}$ (hr)	2.6	3.5	12.2	17.0
CL_E (L/kg)	809	600	118	94
CL_R (L/kg)	426	357	0	0
CL_{NR} (L/kg)	383	243	118	94
$V_{d(ss)}$ (L/kg)	1.95	1.93	1.41	1.93

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

Procainamide Dosing Nomogram
(*FAST ACETYLATORS*)

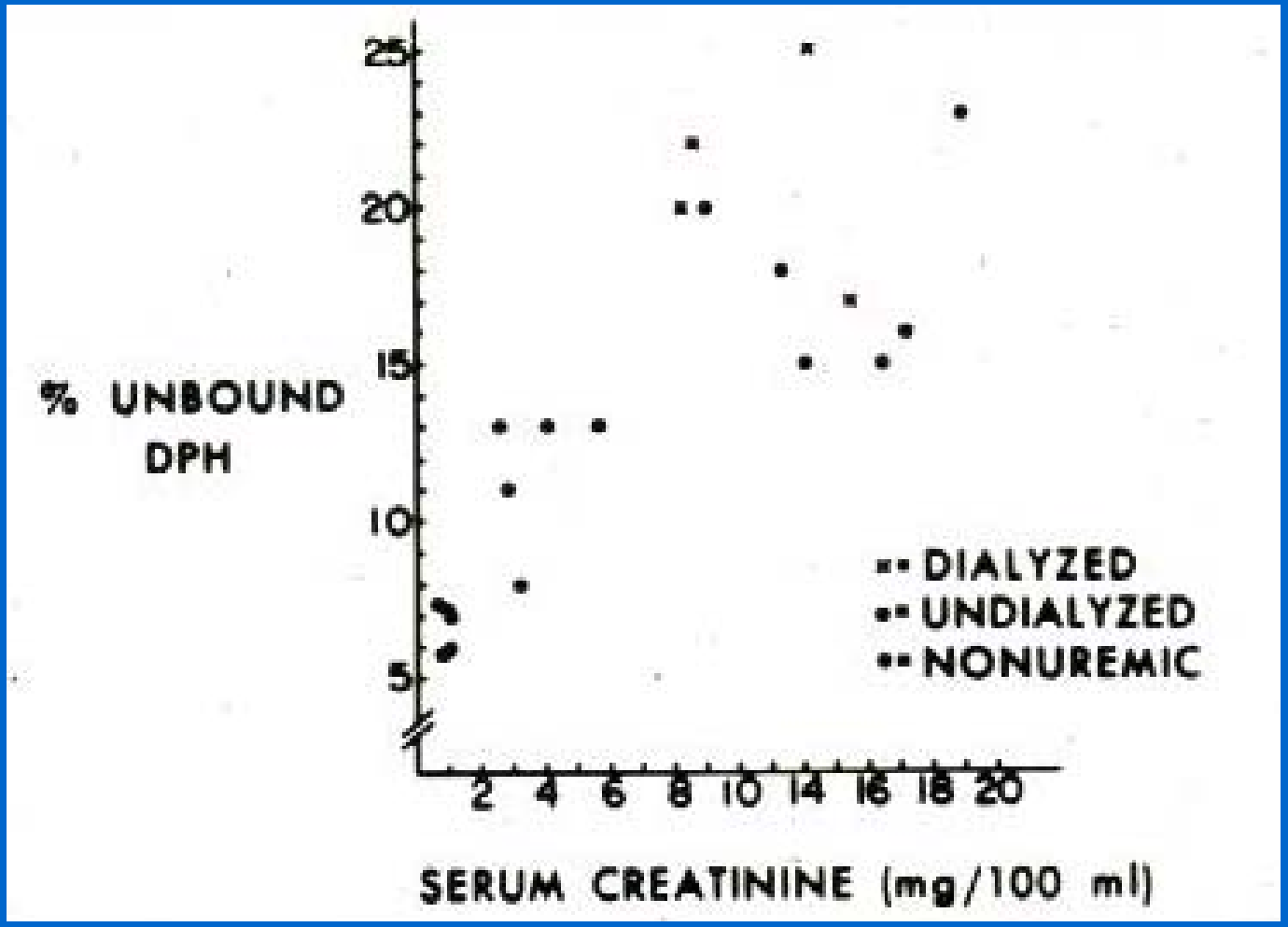


PHENYTOIN *HYDROXYLATION* BY P450



CYP2C9: Major, CYP2C19: Minor

Effect of Renal Disease on *PHENYTOIN PROTEIN BINDING*



PHENYTOIN
*KINETICS IN DIALYSIS PATIENTS**

	NORMALS (N = 4)	UREMIC PATIENTS (N = 4)
% UNBOUND (f_u)	12%	26%
CL_H	2.46 L/hr	7.63 L/hr
CL_{int}	20.3 L/hr	29.9 L/hr NS

$$CL_H = f_u \bullet Cl_{int}, \quad \text{So: } Cl_{int} = CL_H/f_u$$

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

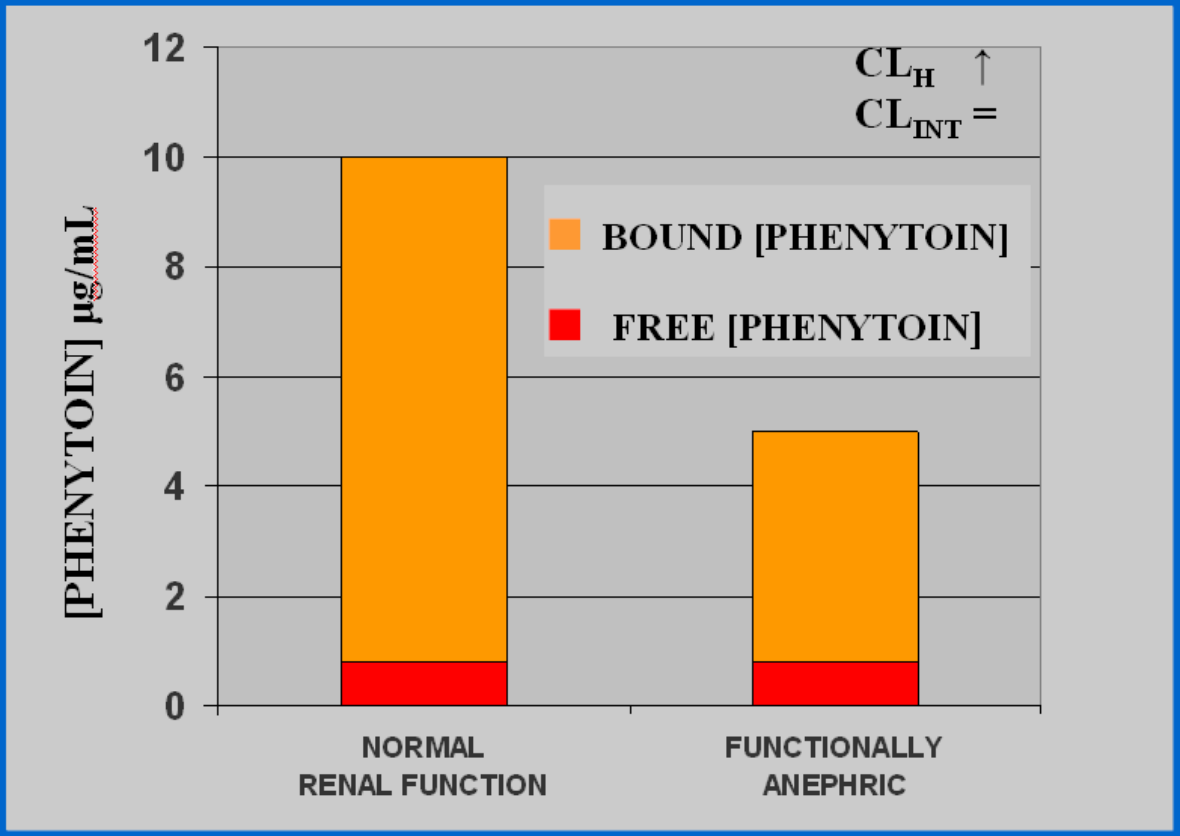
Effect of *PROTEIN BINDING Changes* on Phenytoin Plasma Concentration

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

PHENYTOIN > 98% ELIMINATED BY HEPATIC METABOLISM, SO $CL_E = CL_H$

$$\overline{C}_{ss,\,u} / f_u = \frac{DOSE / \tau}{f_u \; CL_{INT}}$$

FREE AND *TOTAL* PHENYTOIN LEVELS (DOSE = 300 MG/DAY)



THERAPEUTIC RANGE of Phenytoin Levels in *Dialysis Patients*

RISK is that TOTAL levels below the usual range of 10 – 20 µg/mL will prompt inappropriate dose adjustment in dialysis patients.

THERAPEUTIC RANGE FOR DIALYSIS PTS:

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)

GOALS of Renal Disease Effects Lecture

* **EFFECT OF RENAL DISEASE ON DRUG DISTRIBUTION**

  - **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 Binding Changes on *APPARENT DISTRIBUTION VOLUME**

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

Φ = TISSUE/PLASMA PARTITION RATIO

f_u = FRACTION NOT BOUND TO PLASMA PROTEINS

FOR PHENYTOIN: Φ = 10.4

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

PHENYTOIN *DISTRIBUTION* IN *DIALYSIS* PATIENTS*

	NORMALS	UREMIC PATIENTS
% UNBOUND (f_u)	12%†	26%
$V_{d(AREA)}$	0.64 L/kg	1.40 L/kg

† USUAL VALUE IN NORMAL SUBJECTS ~ 9%

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

GOALS OF RENAL DISEASE EFFECTS LECTURE

* **EFFECT OF RENAL DISEASE ON DRUG DISTRIBUTION**

  - **PLASMA PROTEIN BINDING**

    ***EXAMPLE*: PHENYTOIN**

  - **TISSUE BINDING**

    ***EXAMPLE*: DIGOXIN**

IMPAIRED RENAL FUNCTION *REDUCES* DIGOXIN *DISTRIBUTION VOLUME**

$$V_d = 3.84 \bullet \text{wt (kg)} + 3.12 \; CL_{Cr} \text{(mL/min)}$$

* 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:**

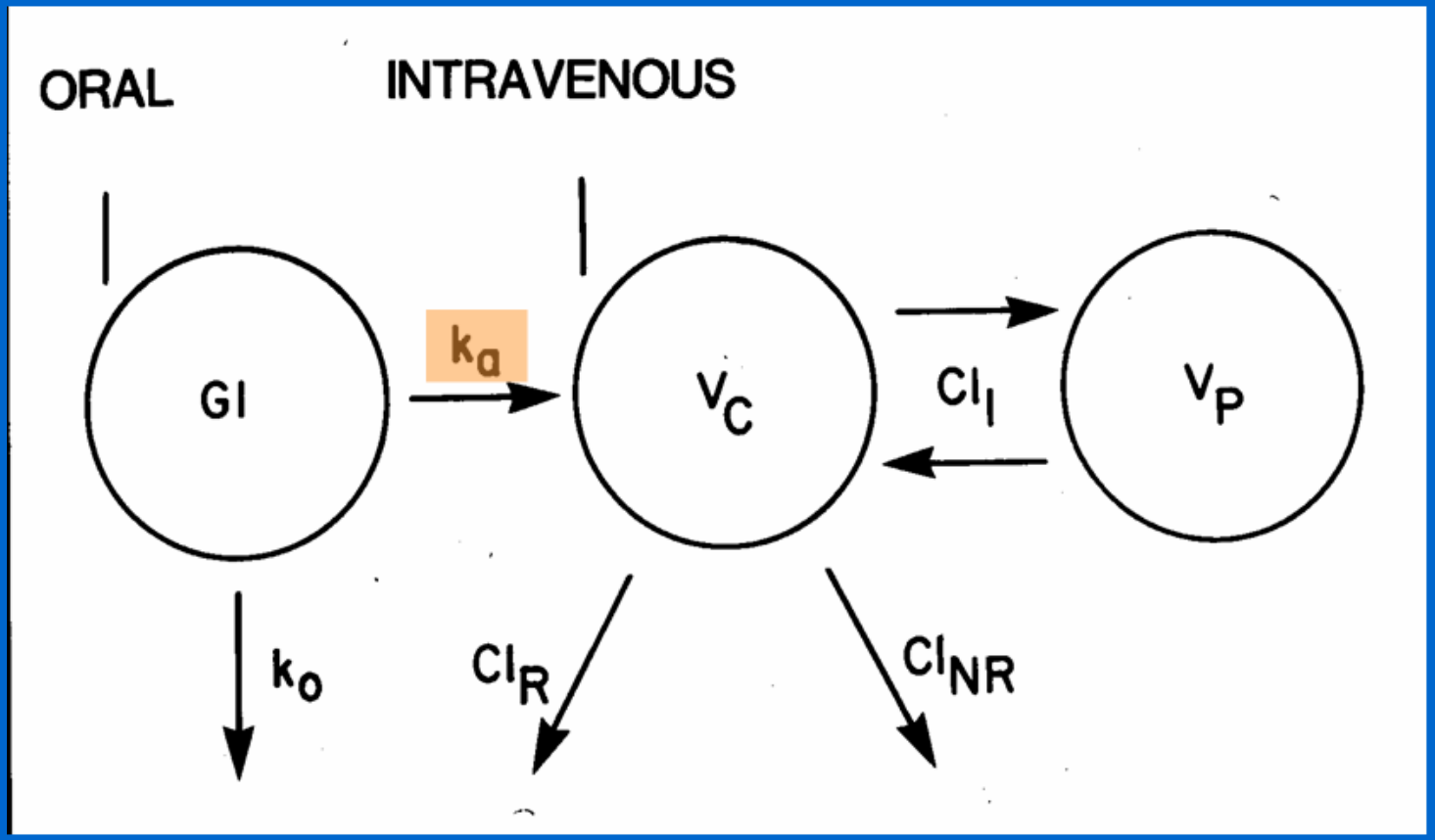
PROPRANOLOL

DEXTROPROPOXYPHENE

CRITERIA FOR NORMAL *ABSORPTION* OF 25 GRAM D-XYLOSE DOSE

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*

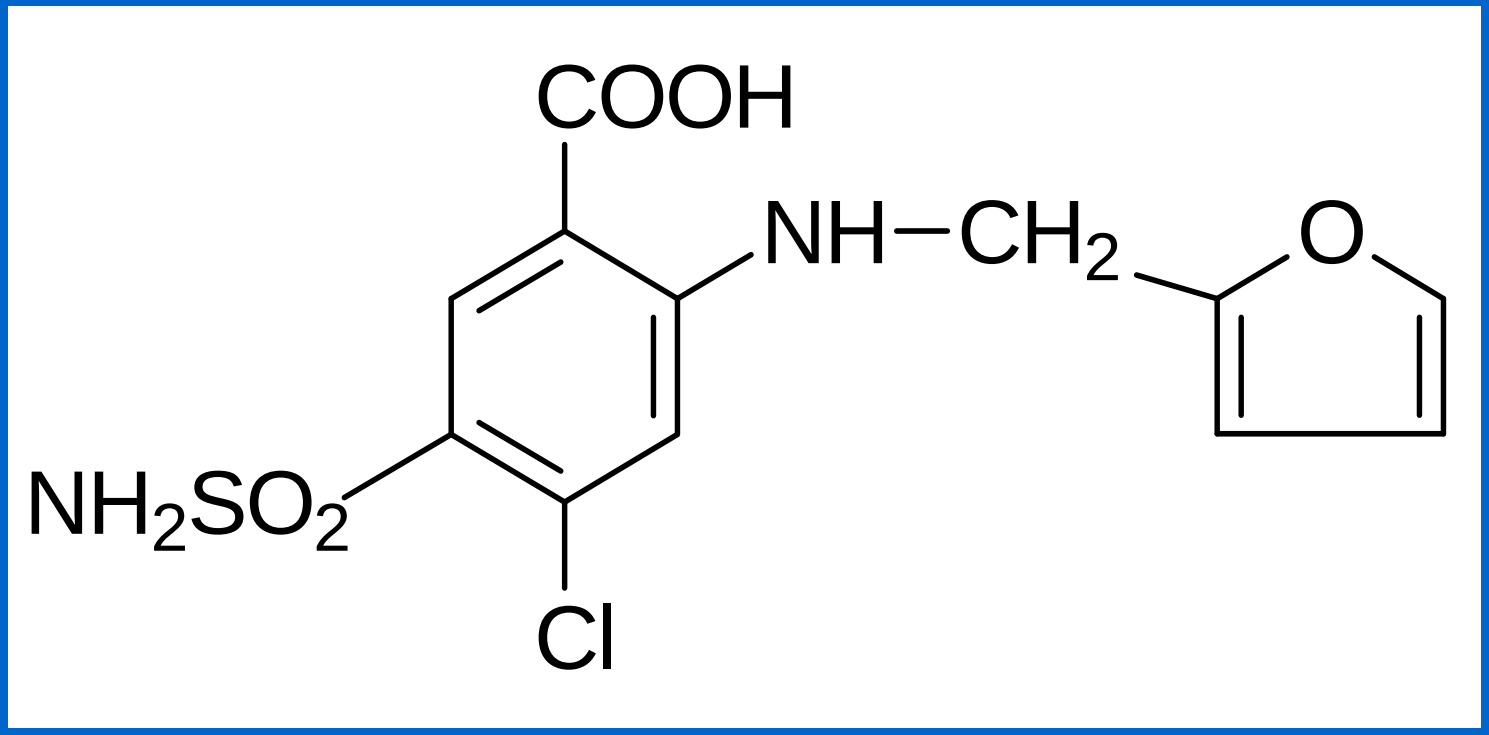
$$F = \frac{k_a}{k_a + k_o}$$

EFFECT OF RENAL DISEASE ON D-XYLOSE *ABSORPTION**

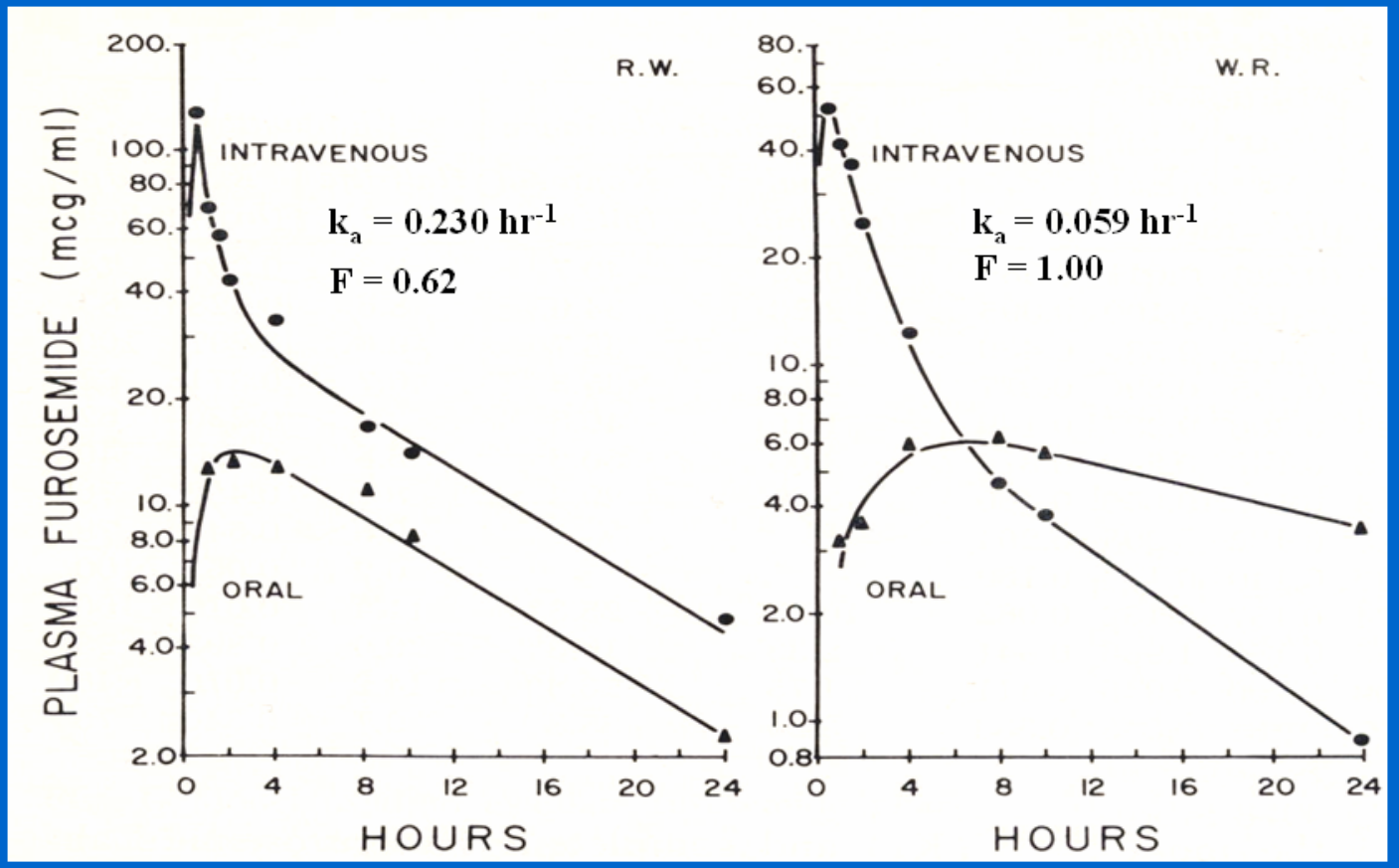
PATIENT GROUP	k_a (hr^{-1})	k_e (hr^{-1})	% DOSE ABSORBED
NORMALS	1.03 ± 0.33	0.49 ± 0.35	69.4 ± 13.6
MODERATE	0.64 ± 0.28	0.19 ± 0.15	77.4 ± 14.8
DIALYSIS	0.56 ± 0.42	0.67 ± 0.61	48.6 ± 13.3

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

FUROSEMIDE

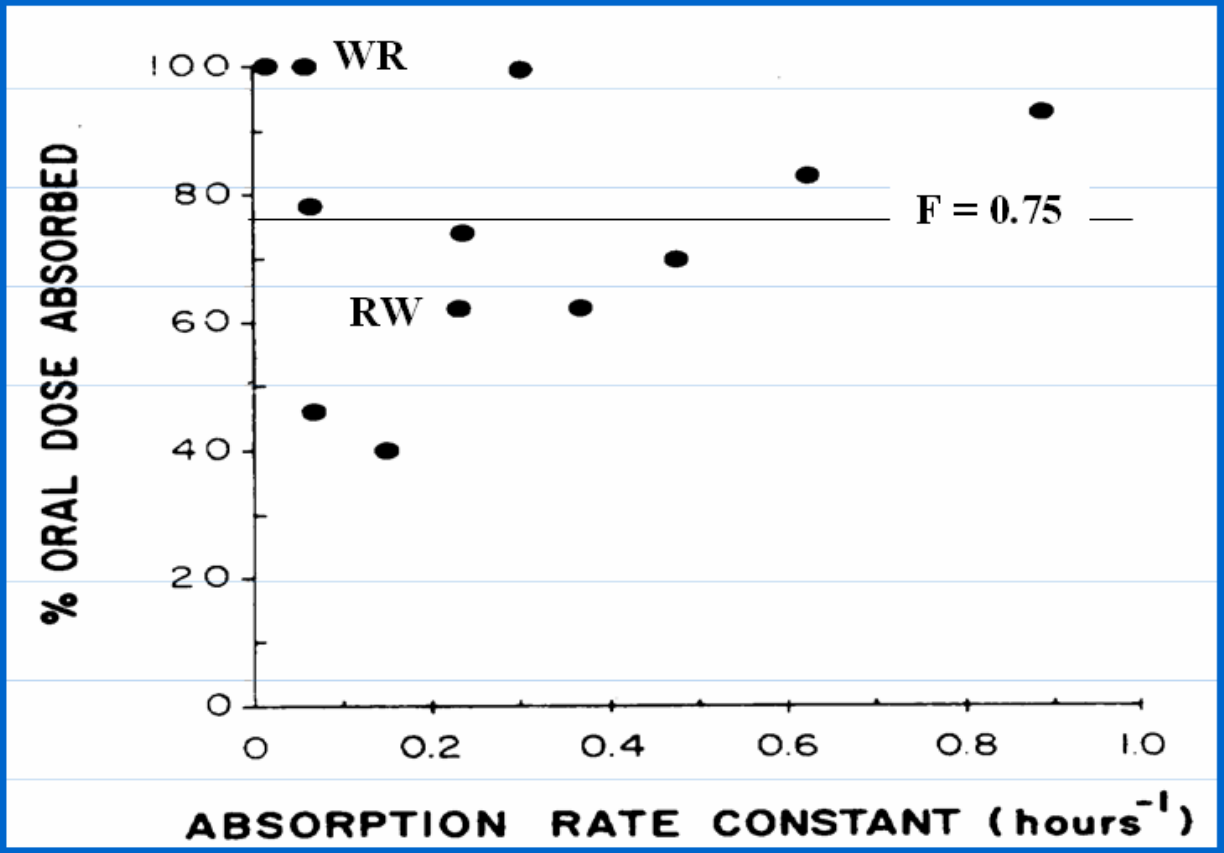


FUROSEMIDE ABSORPTION WITH *ADVANCED RENAL IMPAIRMENT**



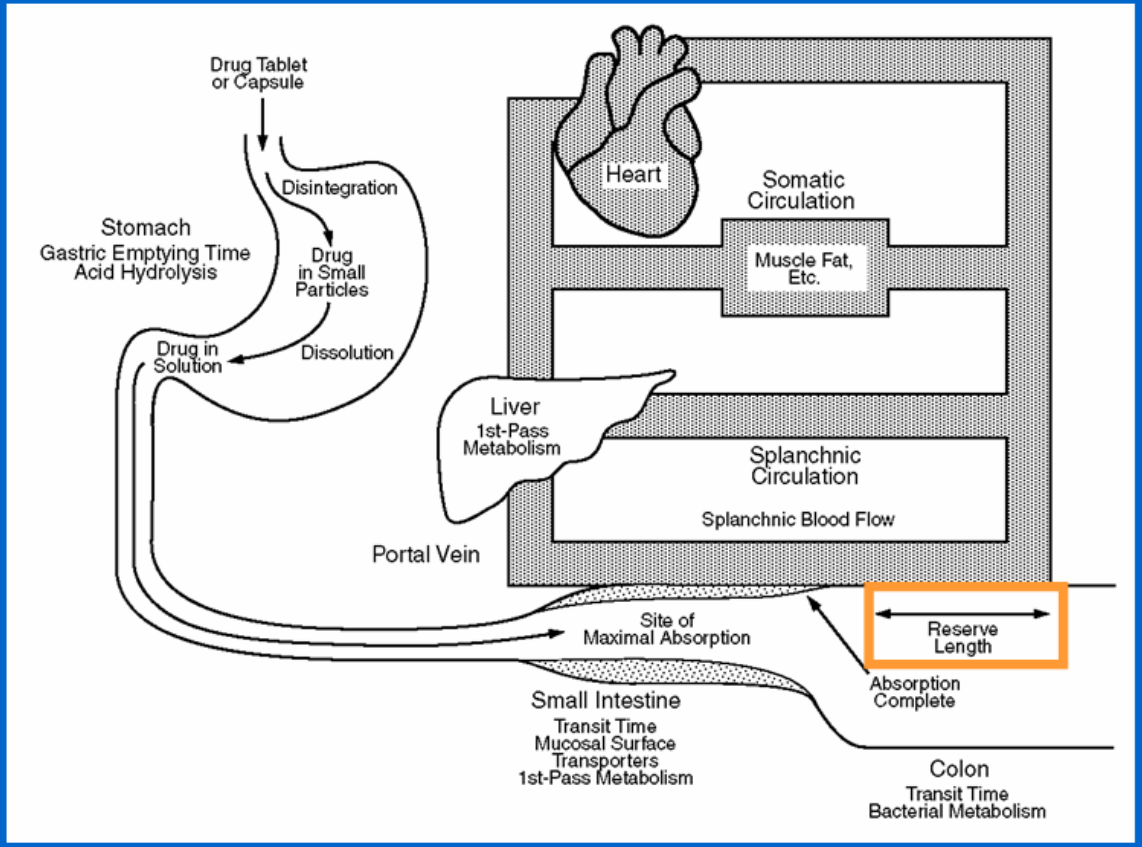
* From Huang CM, et al. Clin Pharmacol Ther 1974;16:659-66.

RELATIONSHIP BETWEEN *FUROSEMIDE* k_a *AND F**

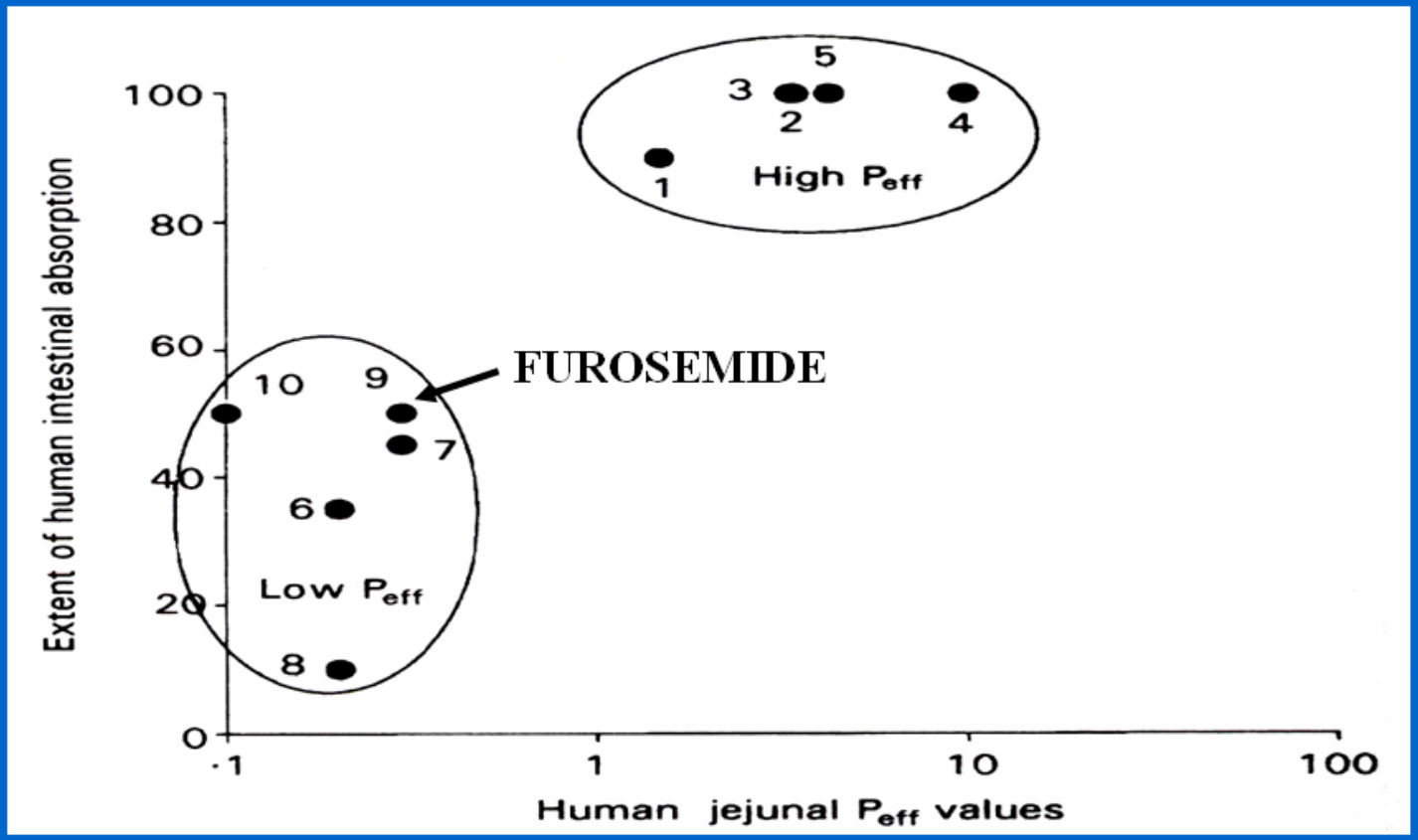


* From Huang CM, et al. Clin Pharmacol Ther 1974;16:659-66.

FACTORS AFFECTING RATE AND EXTENT OF DRUG ABSORPTION



BIOPHARMACEUTIC CLASSIFICATION OF FUROSEMIDE*



* From: Lenneräs. J Pharm Pharmacol 1997;49:627-38.

BIOPHARMACEUTIC DRUG CLASSIFICATION OF FUROSEMIDE *

CLASS IV:

LOW SOLUBILITY-LOW PERMEABILITY

- ***in vitro – in vivo* correlation poor**
- **good bioavailability not expected**

* From: Lenneräs, et al. Pharm Res 1995;12:S396

TORSEMIDE vs. FUROSEMIDE in *Congestive Heart Failure*

	TORSEMIDE	FUROSEMIDE
Bioavailability in CHF *		
F	89.0 ± 8.9%	71.8 ± 29.8%
T_{MAX}	1.1 ± 0.9 hr	2.4 ± 2.5 hr

* From: Vargo D, et al. Clin Pharmacol Ther 1995;57:601-9.

TORSEMIDE vs. FUROSEMIDE in *Congestive Heart Failure*

	TORSEMIDE	FUROSEMIDE
Bioavailability in CHF *		
F	89.0 ± 8.9%	71.8 ± 29.8%
T_{MAX}	1.1 ± 0.9 hr	2.4 ± 2.5 hr
1-Year CHF Therapy**		
CHF Readmit p<0.01	17%	32%
Dose ↑ p<0.01	27%	45%
Dose ↓ p=0.06	32%	22%

* From: Vargo D, et al. Clin Pharmacol Ther 1995;57:601-9.

** From: Murray MD, et al. Am J Med 2001;111:513-20.

CURRENT *REGULATORY PARADOX*

*** *Detailed guidances* for studying kinetics of drug elimination in patients with impaired renal and hepatic function.**

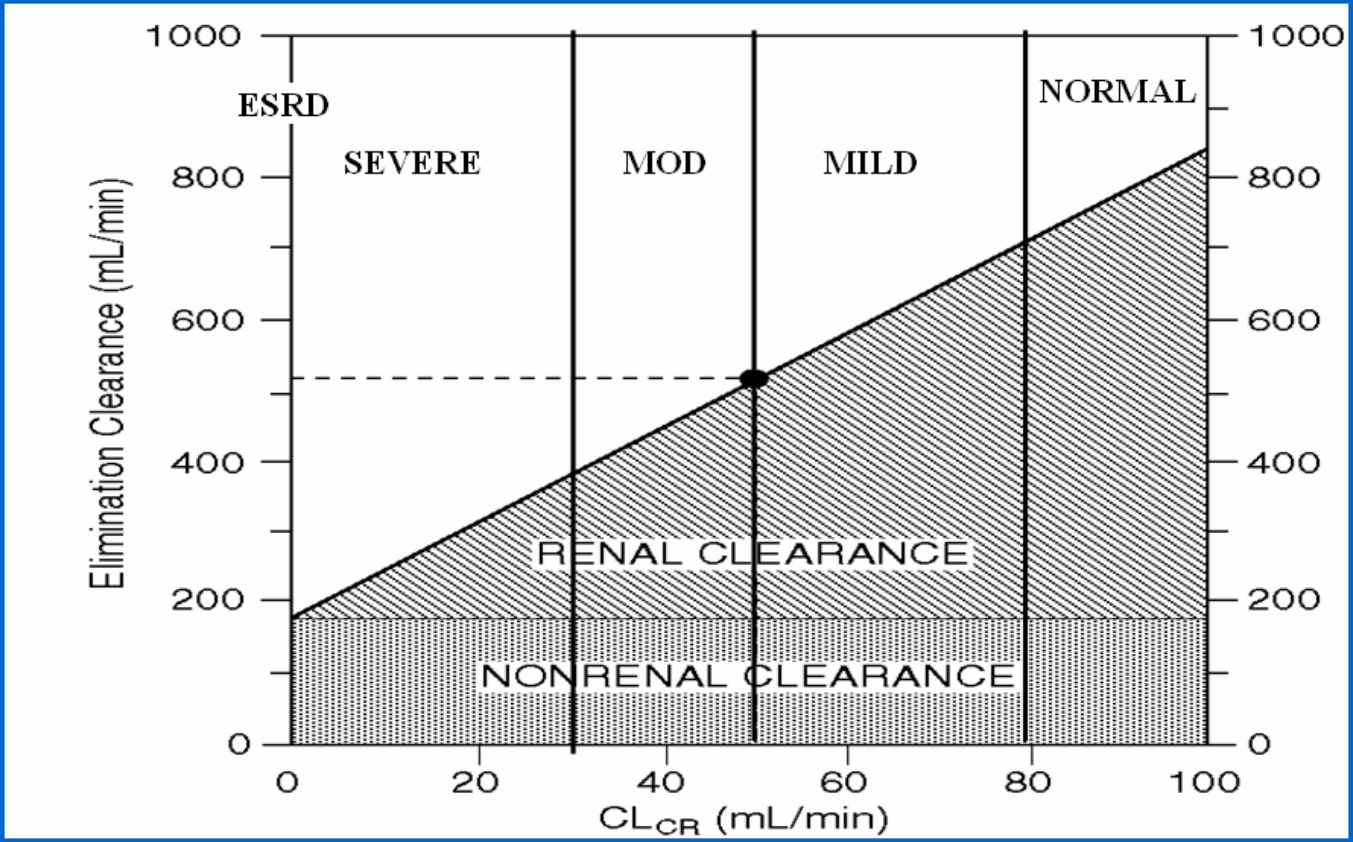
*** *Assumption* that bioavailability studies in *normal subjects* reflect drug absorption in patients.**

FDA *GUIDANCE FOR INDUSTRY*

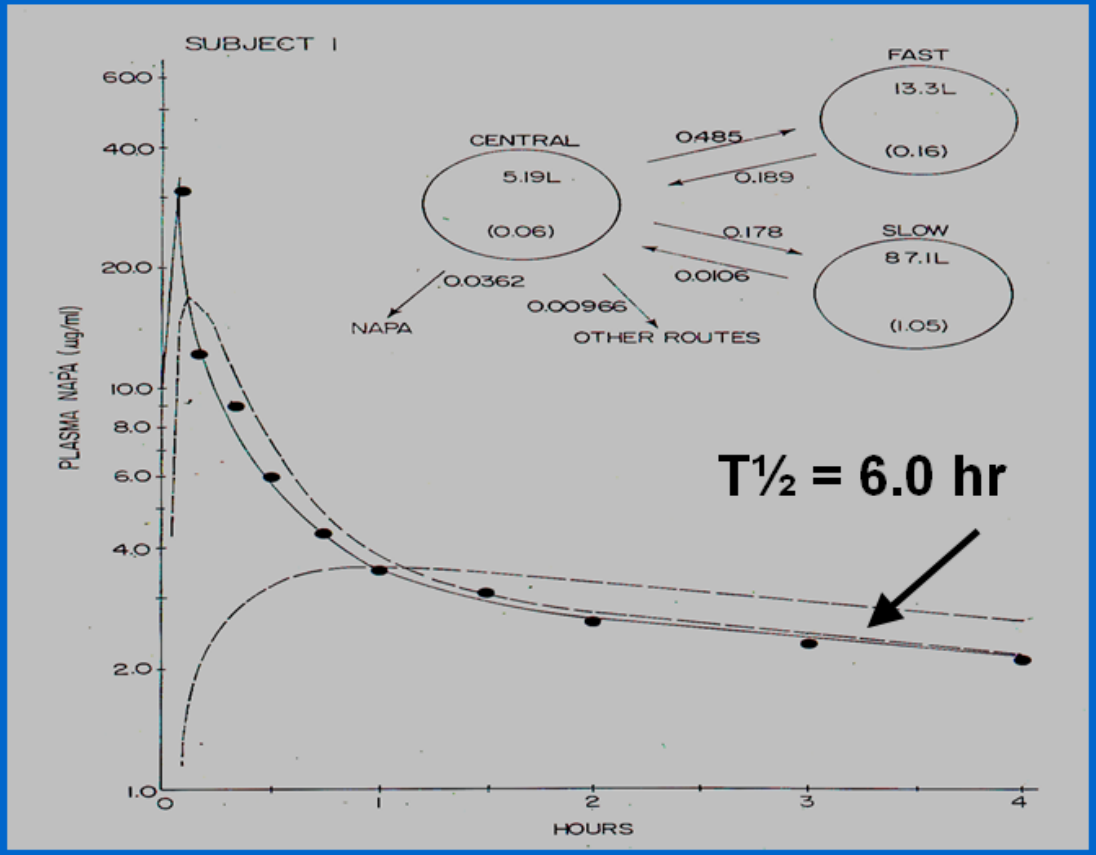
PHARMACOKINETICS IN PATIENTS WITH IMPAIRED RENAL FUNCTION **– Study Design, Data Analysis, and Impact on Dosing and Labeling**

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

BASIC "FULL" STUDY DESIGN

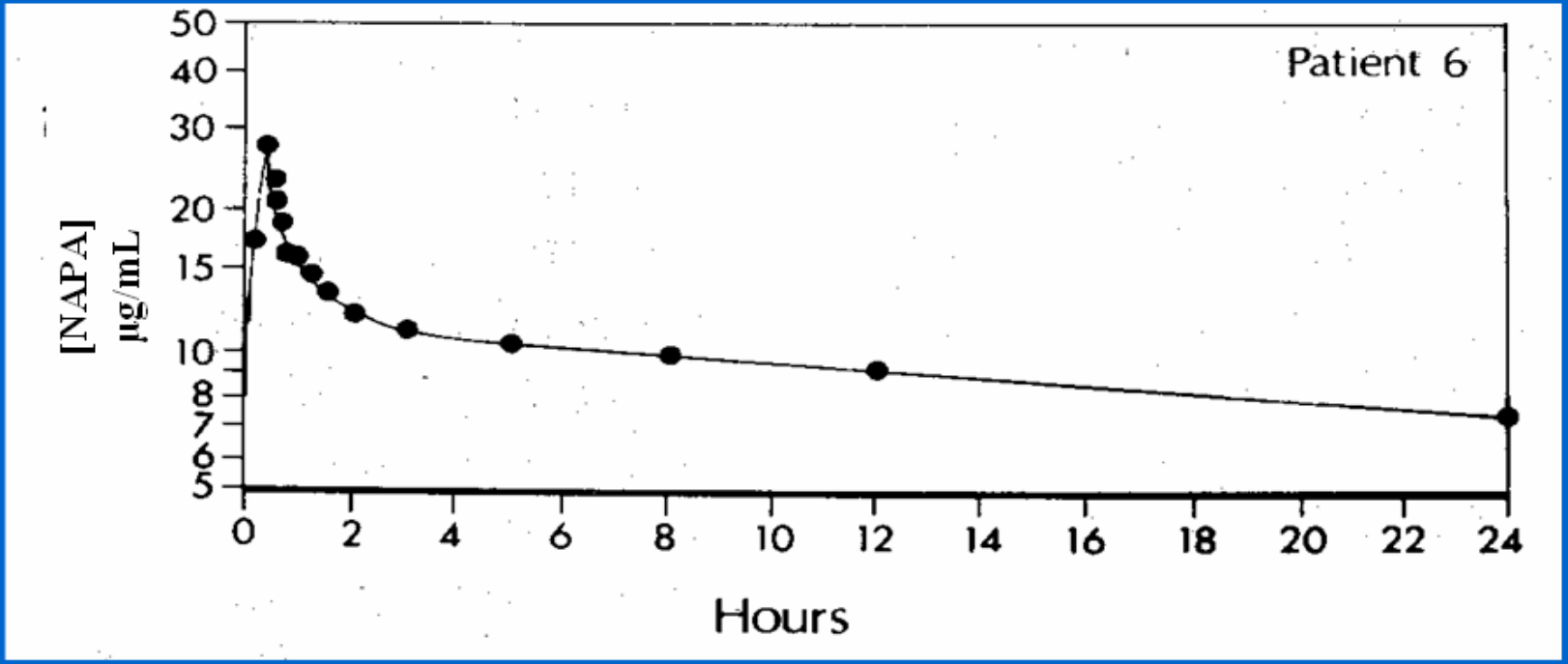


3-COMPARTMENT MAMMILLARY MODEL OF NAPA PK*



* Strong JM, et al. J Pharmacokinet Biopharm 1973;3: 223-5

NAPA PLASMA LEVELS IN A *FUNCTIONALLY ANEPHRIC* PATIENT*



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

NAPA ELIMINATION HALF LIFE IN *FUNCTIONALLY ANEPHRIC* PATIENTS

* HEALTHY SUBJECTS: 6.2 hr

* *PREDICTED* for DIALYSIS PATIENTS: 42.8 hr *

* *MEASURED* in DIALYSIS PATIENTS: 41.9 hr *

See Study Problem at end of Chapter 5.

NOMOGRAM FOR NAPA DOSING