PHARMACOKINETICS IN PATIENTS REQUIRING RENAL REPLACEMENT Rx

PART 1: PK IN PATIENTS REQUIRING HEMODIALYSIS

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FIRST DESCRIPTION OF HEMODIALYSIS IN ANIMALS*

ON THE REMOVAL OF DIFFUSIBLE SUBSTANCES FROM THE CIRCULATING BLOOD OF LIVING ANIMALS BY DIALYSIS

JOHN J. ABEL, LEONARD G. ROWNTREE AND B. B. TURNER

From the Pharmacological Laboratory of the Johns Hopkins University

Received for publication, December 18, 1913

CONTENTS

* From: Abel JJ, et al. J Pharmacol Exp Ther 1914;5:275-317.

WILLEM J. KOLFF, M.D. (1911 -)

ELIMINATION BY DIFFERENT ROUTES

MEASUREMENTS	RENAL	HEPATIC	DIALYSIS
BLOOD FLOW	+*	+*	+
AFFERENT CONC.	+	+	+
EFFERENT CONC.	0	0	+
ELIMINATED DRUG	+	0	+

*not actually measured in routine PK studies

IMPACT OF CL_D

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

GOALS OF DIALYSIS DISCUSSION

DISCUSSION OF DIALYSIS CLEARANCE

- MECHANISTIC - RENKIN APPROACH
- EMPIRICAL
  - FICK EQUATION
  - RECOVERY CLEARANCE

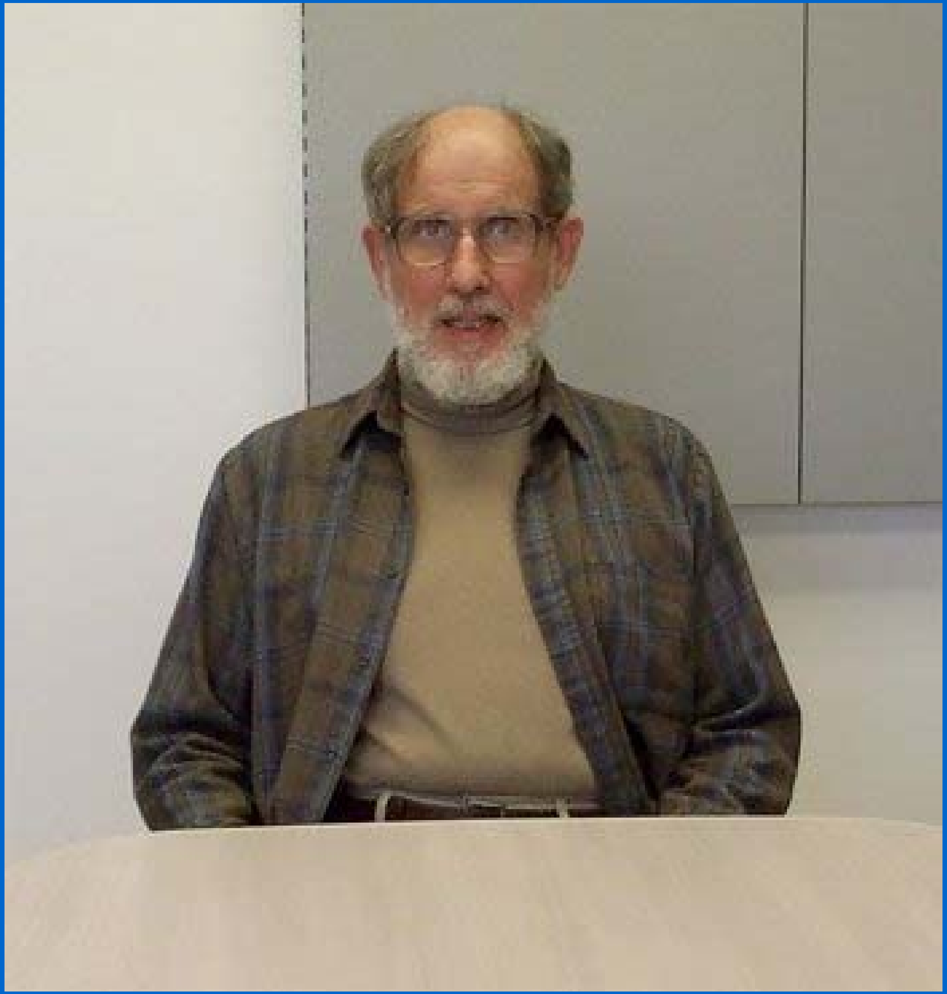
CLINICAL STUDIES OF DIALYSIS PK

- MODEL PROSPECTIVE STUDY
- TREATMENT OF DRUG TOXICITY

PHYSIOLOGIC CHANGES DURING DIALYSIS

- USE OF KINETIC METHODS FOR ANALYSIS
- PATHOPHYSIOLOGIC CONSEQUENCES

EUGENE RENKIN
PROFESSOR EMERITUS AT UC DAVIS



RENKIN DIALYSIS EQUATION*

$$CL_D = Q(1 - e^{-P/Q})$$

Q = DIALYZER BLOOD FLOW

P = PERMEABILITY-SURFACE AREA PRODUCT OF DIALYZING MEMBRANE

NEGLECTS: BOUNDARY EFFECTS, ULTRAFILTRATION

* From Renkin EM. Tr Am Soc Artific Organs 1956;2:102-5

DETERMINANTS OF PERMEABILITY TERM (P or P · S)

- DIALYZER MEMBRANE CHARACTERISTICS
  - MEMBRANE SURFACE AREA
  - MEMBRANE THICKNESS
  - MEMBRANE POROSITY
- DRUG BINDING TO PLASMA PROTEINS
- SOLUTE SIZE AND DIFFUSIVITY

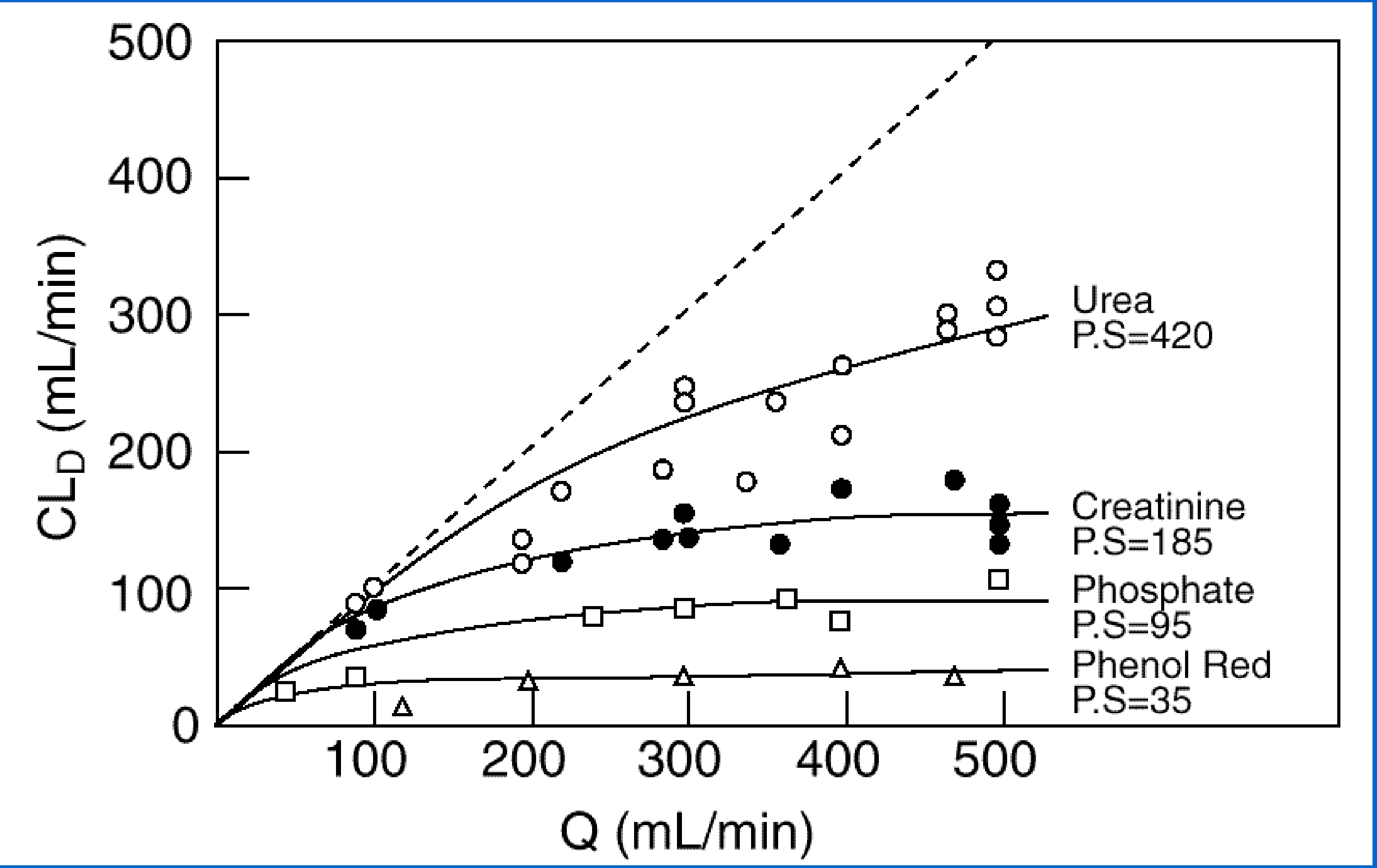
DIALYZER PERMEABILITY VS. FREE WATER DIFFUSION COEFFICIENTS

PROCAINAMIDE/NAPA:

RATIO OF DIALYZER PERMEABILITY COEFFICIENTS*	1.29 ± 0.22
RATIO OF FREE WATER DIFFUSION COEFFICIENTS	1.23

* From Gibson TP et al. Clin Pharmacol Ther 1976;20:720-6.

DIALYSIS CLEARANCE VS. DIALYZER BLOOD FLOW*



* From Renkin EM. Tr Am Soc Artific Organs 1956;2:102-5

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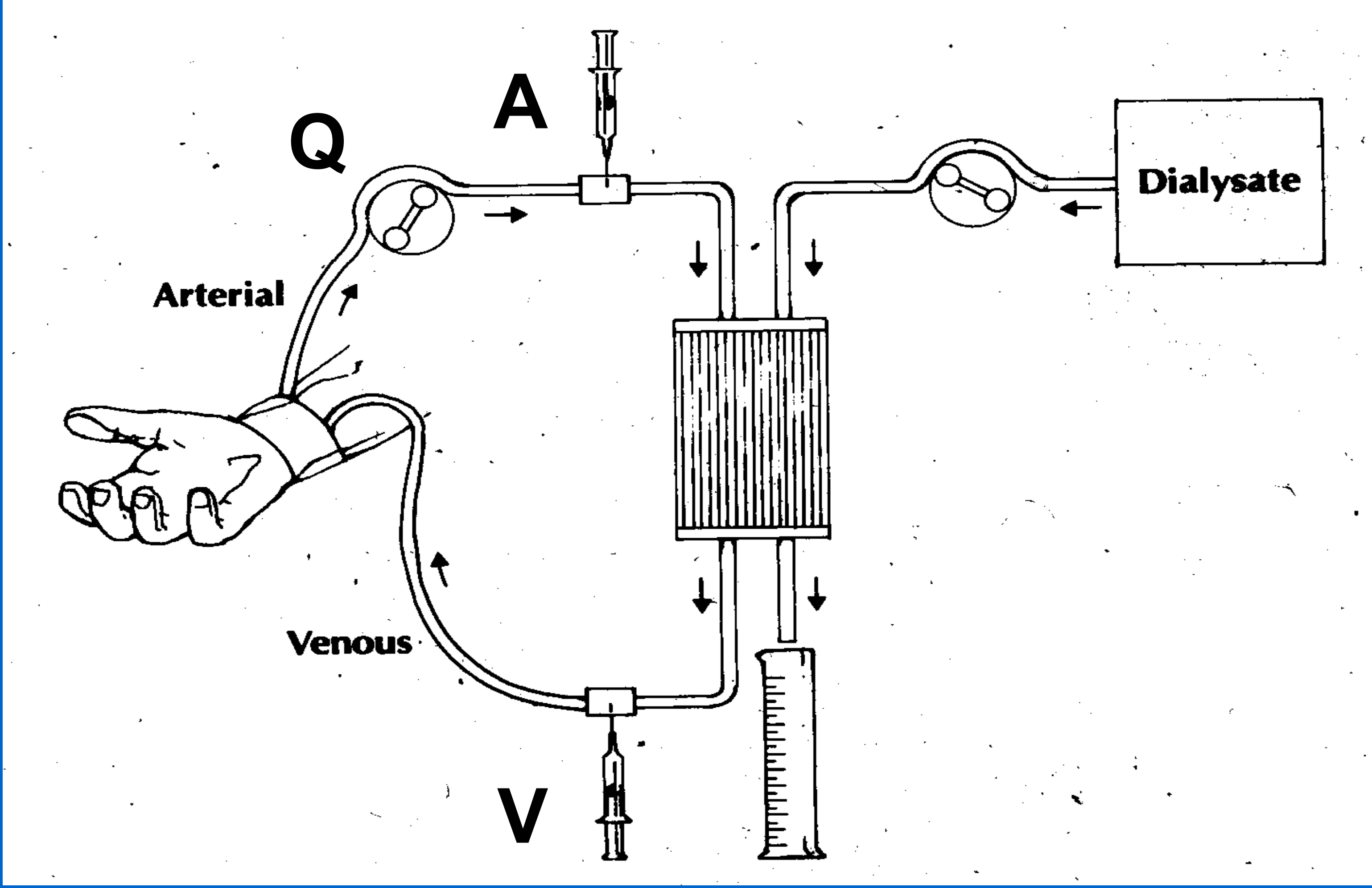
DATA SOURCES FOR FICK EQUATION



FICK EQUATION

$$CL = Q \left[\frac{A - V}{A} \right]$$

$$E = \left[\frac{A - V}{A} \right]$$

Q = DIALYZER BLOOD FLOW
A = CONCENTRATION IN BLOOD COMING TO DIALYZER
V = CONCENTRATION IN BLOOD LEAVING DIALYZER
E = EXTRACTION RATIO

EXTRACTION RATIO

Renkin Equation:

$$E = \left[1 - e^{-P/Q}\right]$$

Fick Equation:

$$E = \left[\frac{A - V}{A}\right]$$

In Each Case:

$$CL = Q \bullet E$$

RECOVERY CLEARANCE

THE GOLD STANDARD

$$CL = \frac{U \cdot V}{P \cdot t}$$

U = DIALYSATE CONCENTRATION
V = DIALYSATE VOLUME
t = DIALYSIS TIME
P = MEAN PLASMA CONCENTRATION

TWO DIALYSIS MYTHS

- NEED TO USE BLOOD CONCENTRATIONS WHEN CALCULATING BLOOD CLEARANCE

  BUT PLASMA CONCENTRATIONS PROPORTIONAL TO BLOOD CONCENTRATIONS, SO MAKES NO DIFFERENCE IN A/[A + V] RATIO

- NEED TO USE PLASMA FLOW WHEN CALCULATING PLASMA CLEARANCE

PLASMA VS. BLOOD CLEARANCE

RECOVERY :

$$CL_P = \frac{U \bullet V}{P} \qquad CL_B = \frac{U \bullet V}{B}$$

FICK :

$$CL_P = Q_{PK}\left(\frac{A - V}{A}\right) \qquad CL_B = Q_B\left(\frac{A - V}{A}\right)$$

$$\text{IF } B > P:\ CL_P > CL_B,\quad \text{SO}:\ Q_{PK} > Q_B > Q_P$$

NAPA IN RBC IS DIALYZED

FLOW PARAMETER	MEAN VALUE mL/min
Q_{PK}	223
Q_{MEAS}	195 ($p < 0.2$)
Q_{EFF}*	217 ($p > 0.2$)

* $Q_{EFF} = [\,(1 - Hct) + (RBC/P)\,(HCT)\,]\,Q_{MEAS}$

DIALYSIS SATURATION VS. RECOVERY CLEARANCE

DIALYSIS SATURATION ($EC = C_d/C_p$):

$$CL_D = Q_d \frac{C_d}{C_p}$$

RECOVERY CLEARANCE:

$$CL_D = \frac{UV}{P\tau} = \frac{C_d V_d}{C_p \tau}$$

BUT:

$Q_d = \frac{V_d}{\tau}$ *SO EXPRESSIONS ARE EQUIVALENT*

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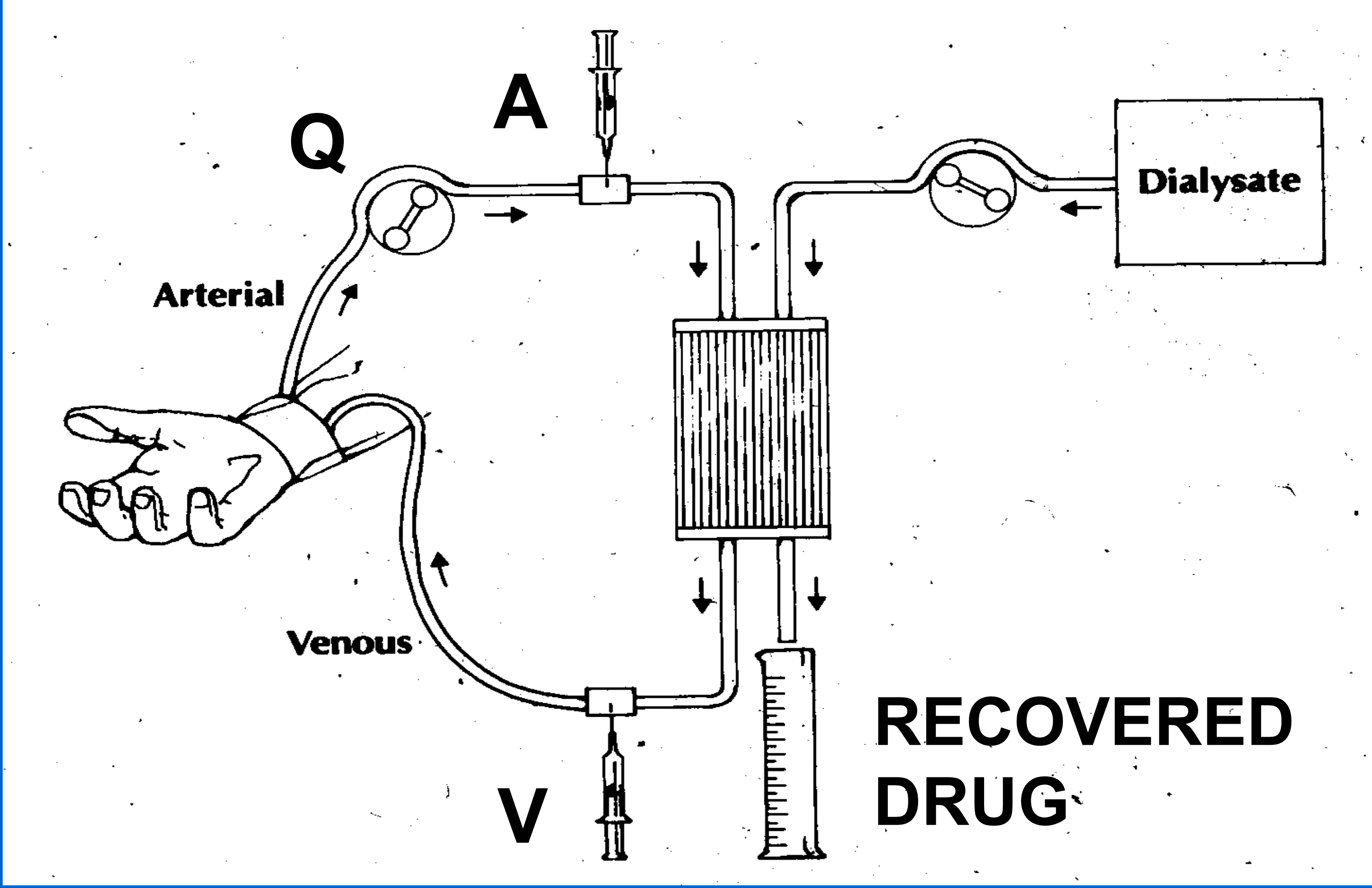
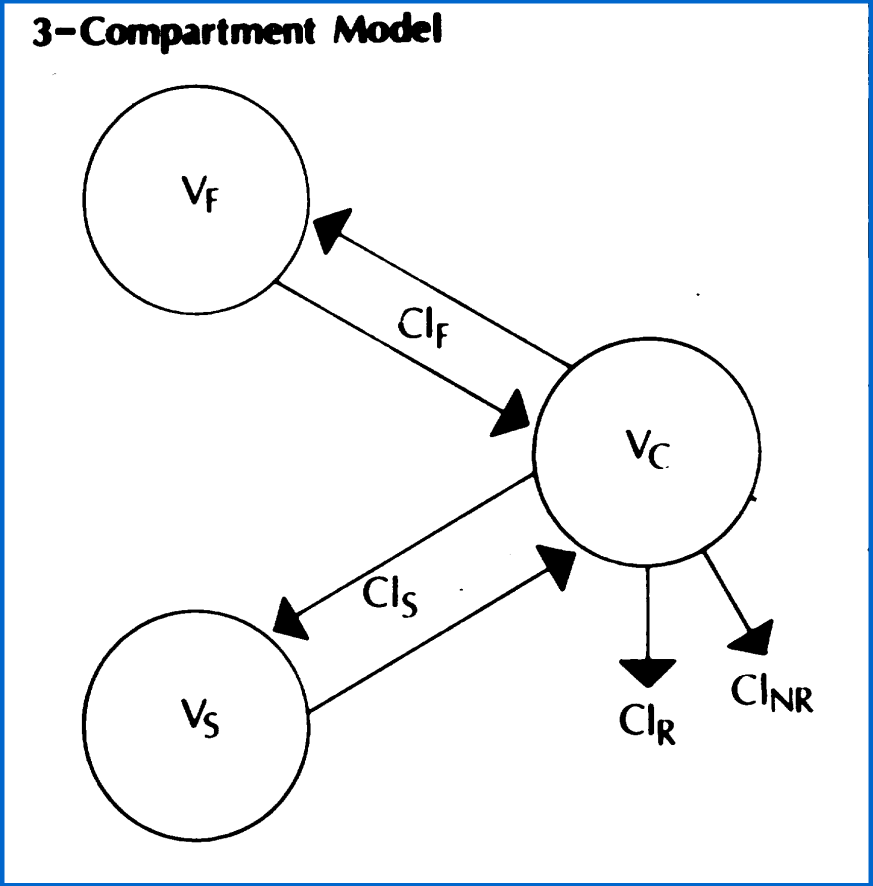
DATA SOURCES FOR RIGOROUS PK ANALYSIS

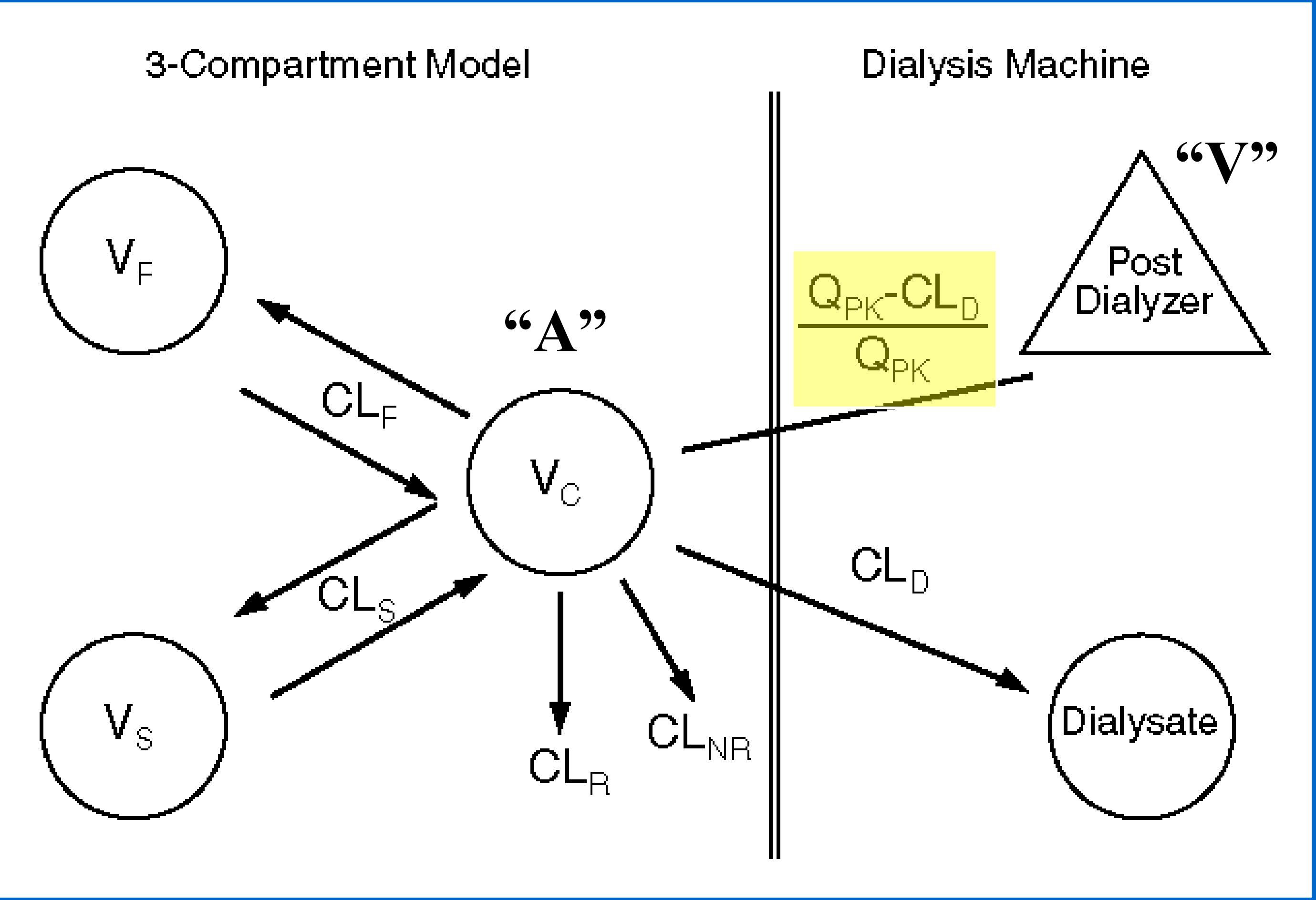


KINETIC MODEL USED TO ANALYZE HEMODIALYSIS DATA*



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

KINETIC MODEL USED TO ANALYZE HEMODIALYSIS DATA*



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

FICK CLEARANCE EQUATION

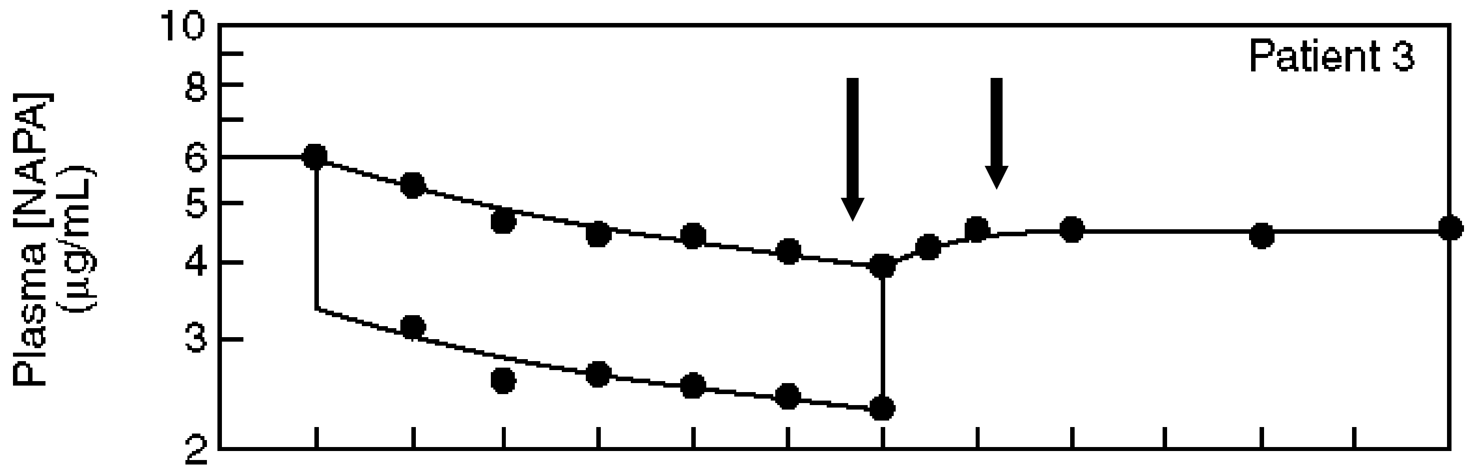
$$CL = Q\left[\frac{A - V}{A}\right]$$

$$CLA = QA - QV$$

$$QV = QA - CLA$$

$$V = \left[\frac{Q - CL}{Q}\right]A$$

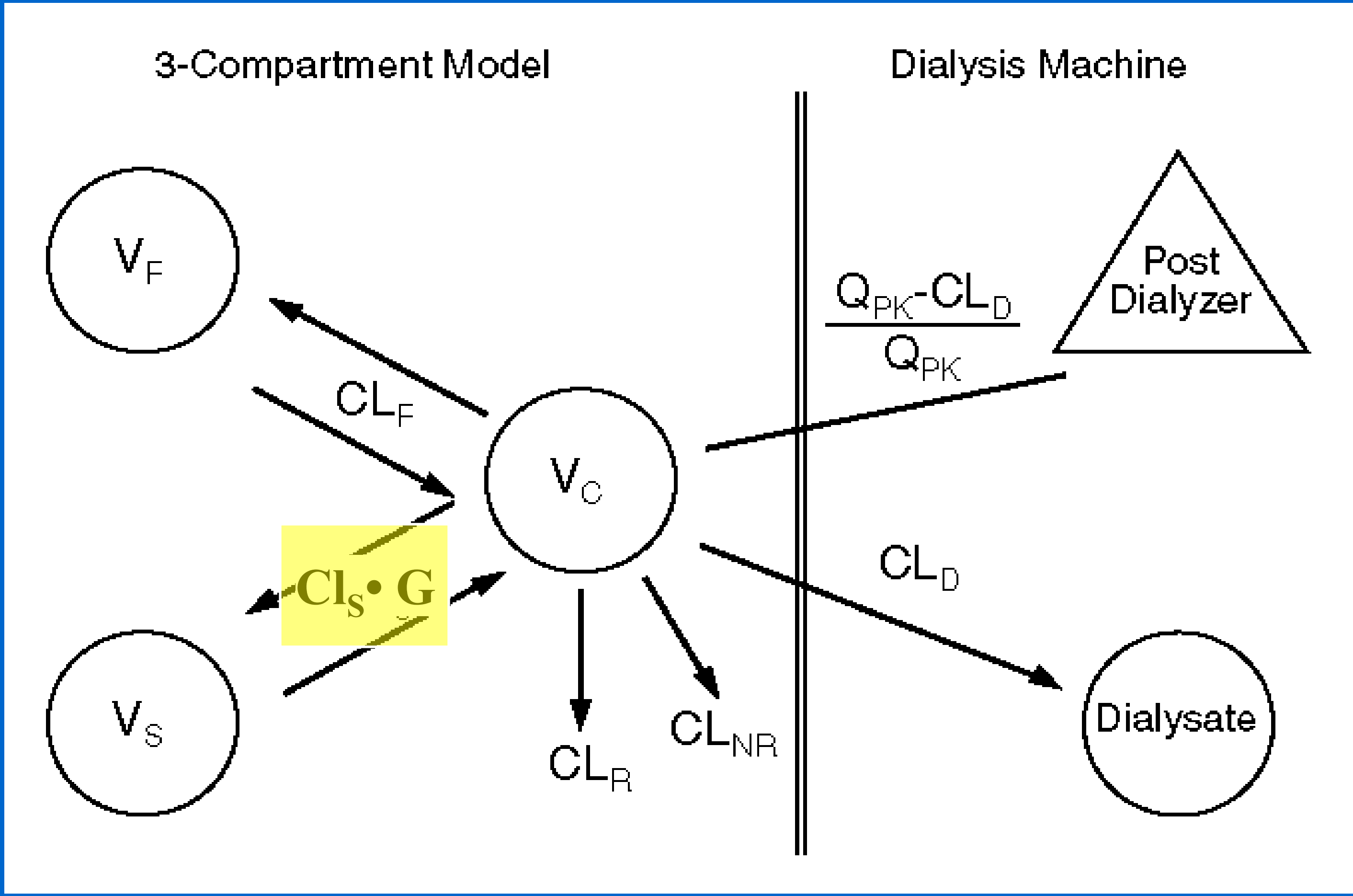
TWO PROBLEMS WITH FIXED-PARAMETER MODEL*



1. **<u>DURING DIALYSIS</u>: [A] AND [V] DROP MORE THAN EXPECTED FROM DRUG RECOVERY**
2. **<u>AFTER DIALYSIS</u>: CONCENTRATION REBOUND IS LESS THAN EXPECTED**

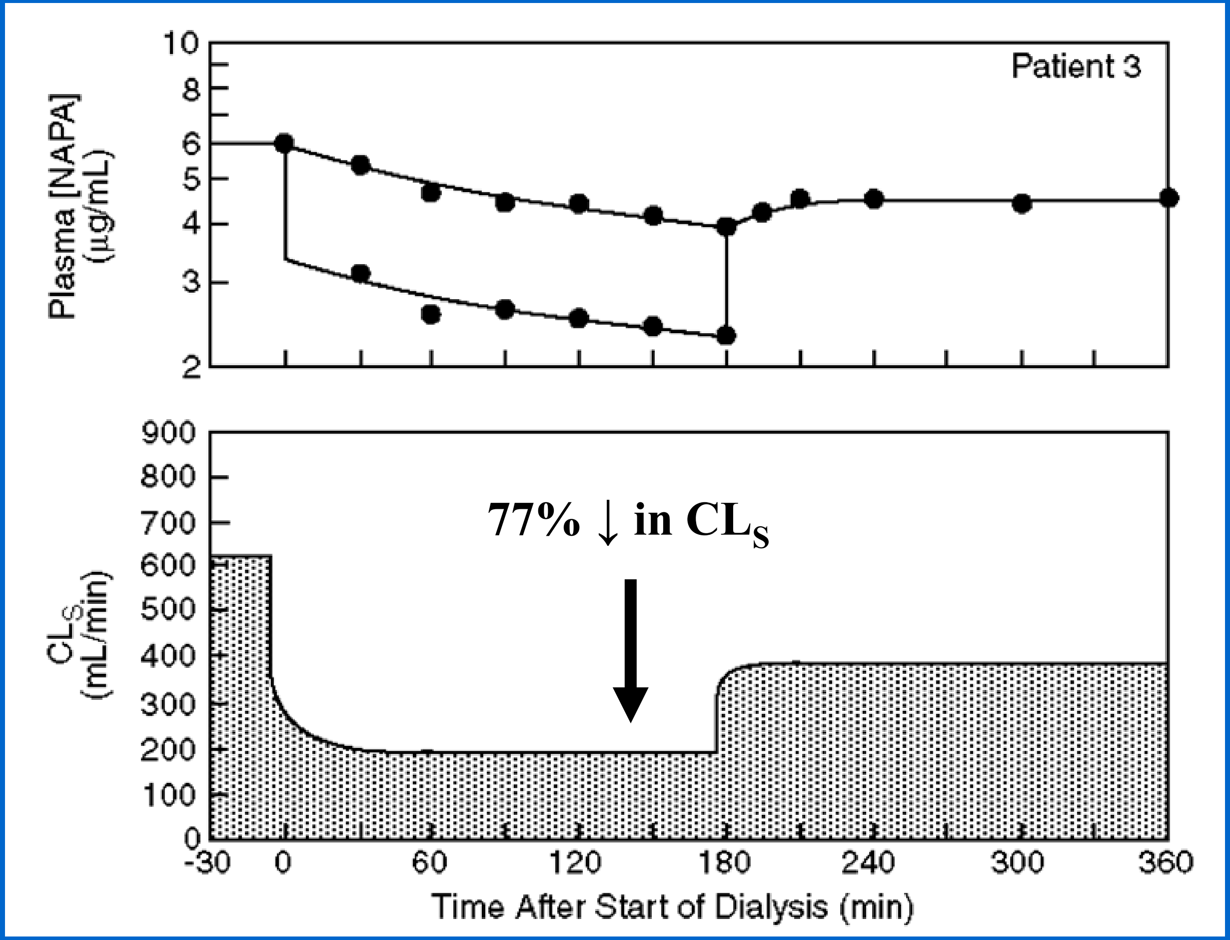
* From Stec GP, et al. Clin Pharmacol Ther 1979;26:618-28.

KINETIC MODEL USED TO ANALYZE HEMODIALYSIS DATA*



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

REDUCTION IN CL_S DURING AND AFTER HEMODIALYSIS*



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

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CASE HISTORY

A 67 year-old woman became lethargic and confused and developed hypotension, renal insufficiency, junctional tachycardia and intraventricular conduction delay after ingesting an estimated 7gm of procainamide (PA). Plasma PA and NAPA concentrations were 57 µg/mL and 55 µg/mL, respectively.

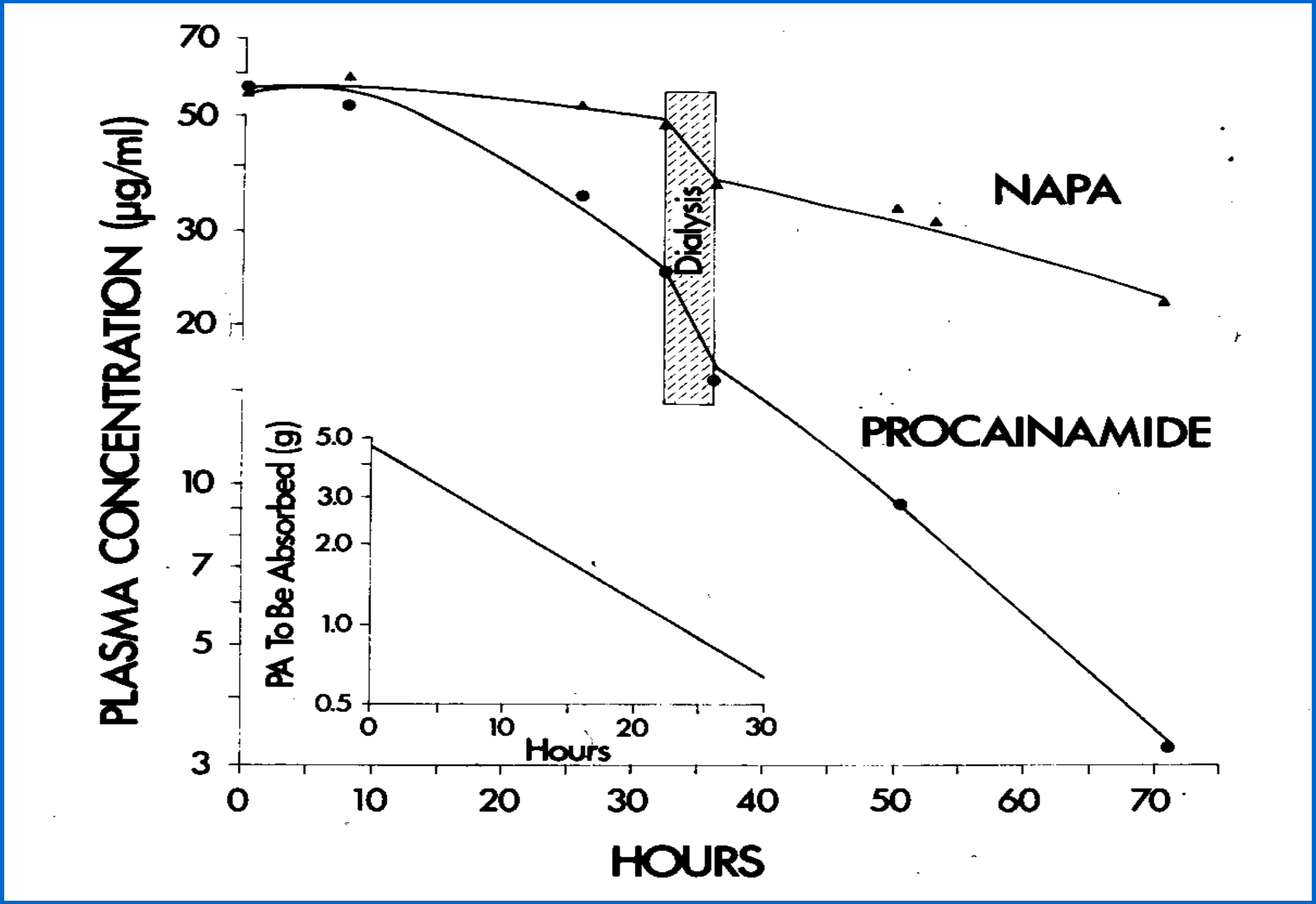
CASE HISTORY (cont.)

Hemodialysis was performed for 4 hr. By the end of the second hour BP was maintained in the range of 110/80 mm Hg without vasopressor therapy. At the end of dialysis, the patient was alert and oriented although only 340 mg of PA and 470 mg of NAPA had been removed by this procedure.

DIALYSIS CASE HISTORY (cont.)

Fifteen hours after dialysis, PA and NAPA levels were 9.2 µg/mL and 33 µg/mL, respectively. The patient had returned to normal sinus rhythm with QRS = 0.12 sec.

KINETIC ANALYSIS OF HEMODIALYSIS FOR PROCAINAMIDE TOXICITY*



* From: Atkinson AJ Jr, et al. Clin Pharmacol Ther 1976;20:585-92.

CRITERION FOR DIALYSIS EFFICACY*

$$CL_{EC} > 30\% \, [CL_{R} + CL_{NR}]$$

* Levy G. Am J Med 1977;62:461-5.

WAS DIALYSIS EFFICACIOUS?

- DIALYSIS INCREASED DRUG CLEARANCE

  PA – TWO FOLD

  NAPA – 3.8 FOLD

- BUT 4 hr OF DIALYSIS REMOVED < 1 gm of 7 gm DOSE

  340 mg PA

  470 mg NAPA

- HOWEVER, BLOOD LEVELS FELL SUBSTANTIALLY

  PA: 25.7 µg/mL → 15.5 µg/mL

  NAPA: 47.0 µg/mL → 35.5 µg/mL

AND PATIENT'S CONDITION STABILIZED

PA & NAPA KINETICS IN TOXIC PATIENT

	NORMAL		PATIENT	
	PA	NAPA	PA	NAPA
$t_{1/2}$ (hr)	2.5	6.2	10.5	35.9
$V_{d\beta}$ (L/kg)	1.80	1.76	0.76	0.63
CL_E (mL/min)	590	233	66.8	16.1
CL_D (mL/min)			68.3	45.8

ESTIMATION OF V_d

Question: Why was distribution volume estimate so much lower in patient than in normal subjects?

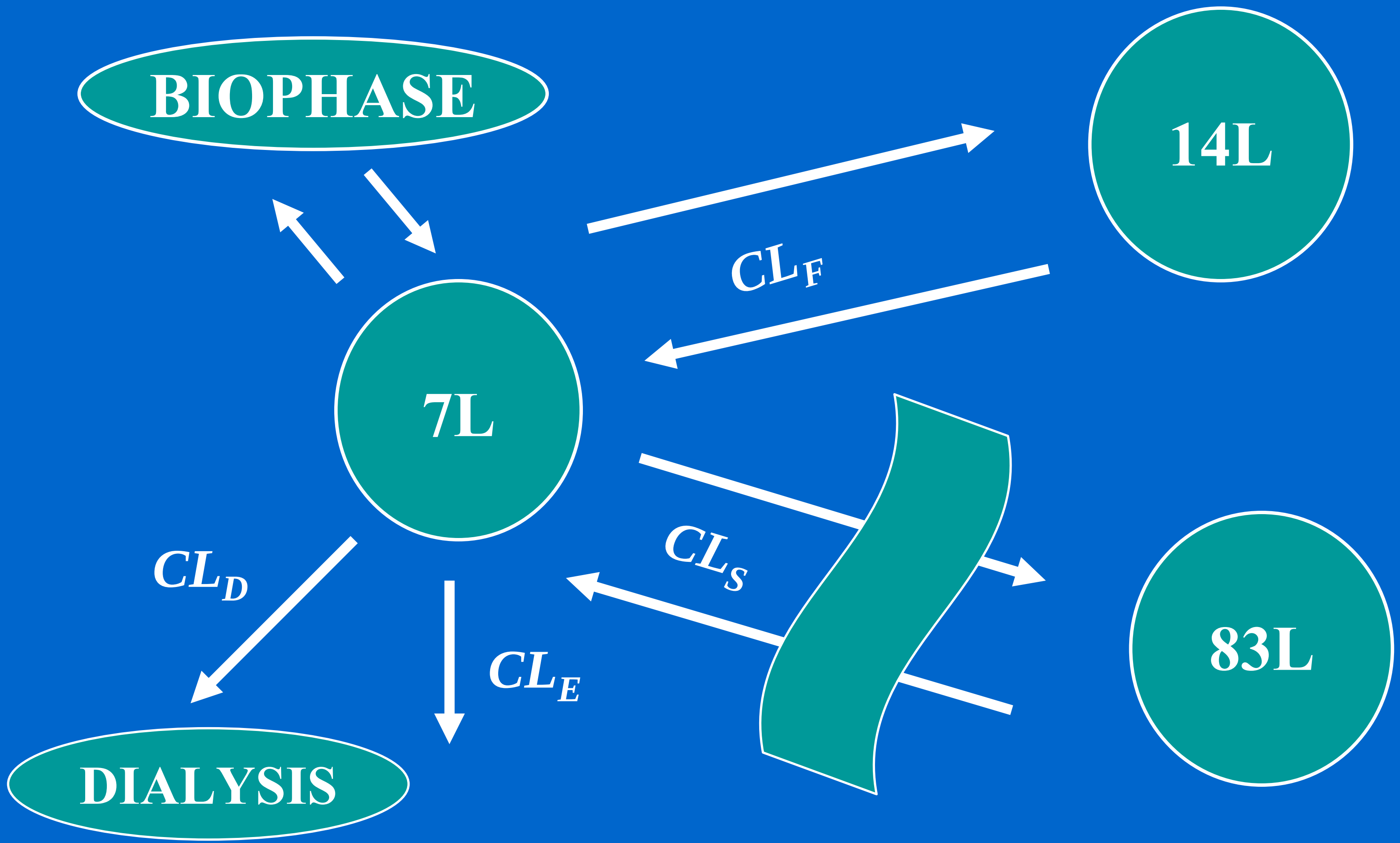
USUAL V_d ESTIMATE:

$$V_d = \frac{\text{DOSE GIVEN}}{\Delta\ \text{CONCENTRATION}}$$

DIALYSIS V_d ESTIMATE:

$$V_d = \frac{\text{DRUG REMOVED}}{\Delta\ \text{CONCENTRATION}}$$

SEQUESTRATION OF DRUG IN SOMATIC TISSUES



EFFICACY OF EXTRACORPOREAL TREATMENT OF DRUG TOXICITY

- TOTAL EXTENT OF DRUG REMOVAL MAY BE COMPROMIZED BY ↓ CL_S.
- ↓ CL_S FROM SOMATIC TISSUES CAN ACCELERATE ↓ IN DRUG CONCENTRATION TO WHICH VITAL ORGANS (CNS, HEART) ARE EXPOSED AND RESULT IN A BENEFICIAL CLINICAL RESPONSE > EXTENT OF DRUG REMOVAL.
- ↓ CL_S FROM SOMATIC TISSUES ALSO ATTENUATES POST-DIALYSIS REBOUND.

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WHY DOES $CL_S \downarrow$ DURING DIALYSIS ?

POSSIBILITIES:

- CAPILLARY BLOOD FLOW DECREASES
- CAPILLARY P●S PRODUCT DECREASES
- BOTH DECREASE

RENKIN EQUATION*

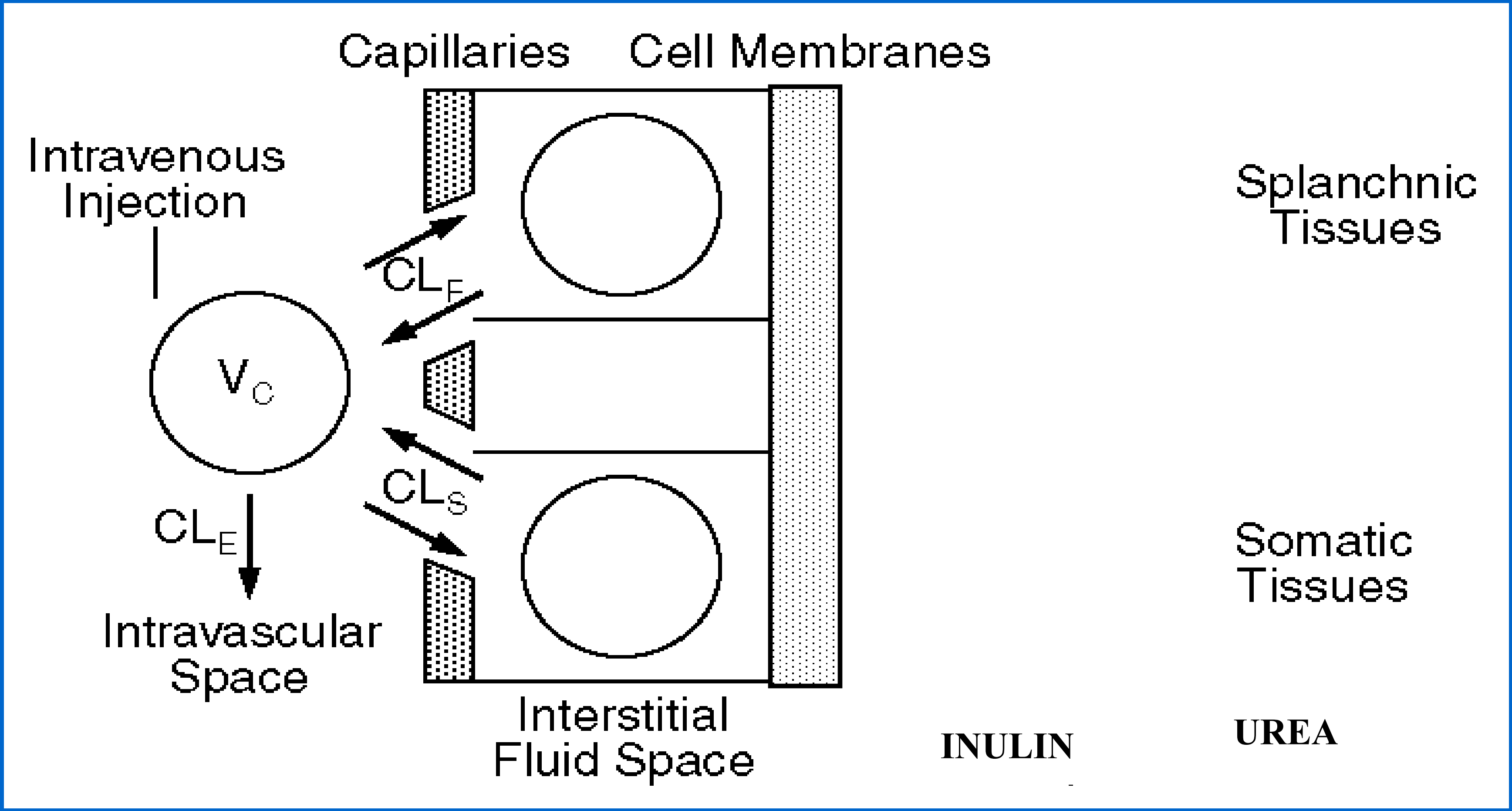
$$CL = Q\left(1 - e^{-P/Q}\right)$$

Q = capillary blood flow

P = capillary permeability coefficient-surface area product (sometimes denoted P•S).

* From Renkin EM. Am J Physiol 1953;183:125-36.

MULTICOMPARTMENTAL MODEL OF INULIN AND UREA KINETICS*

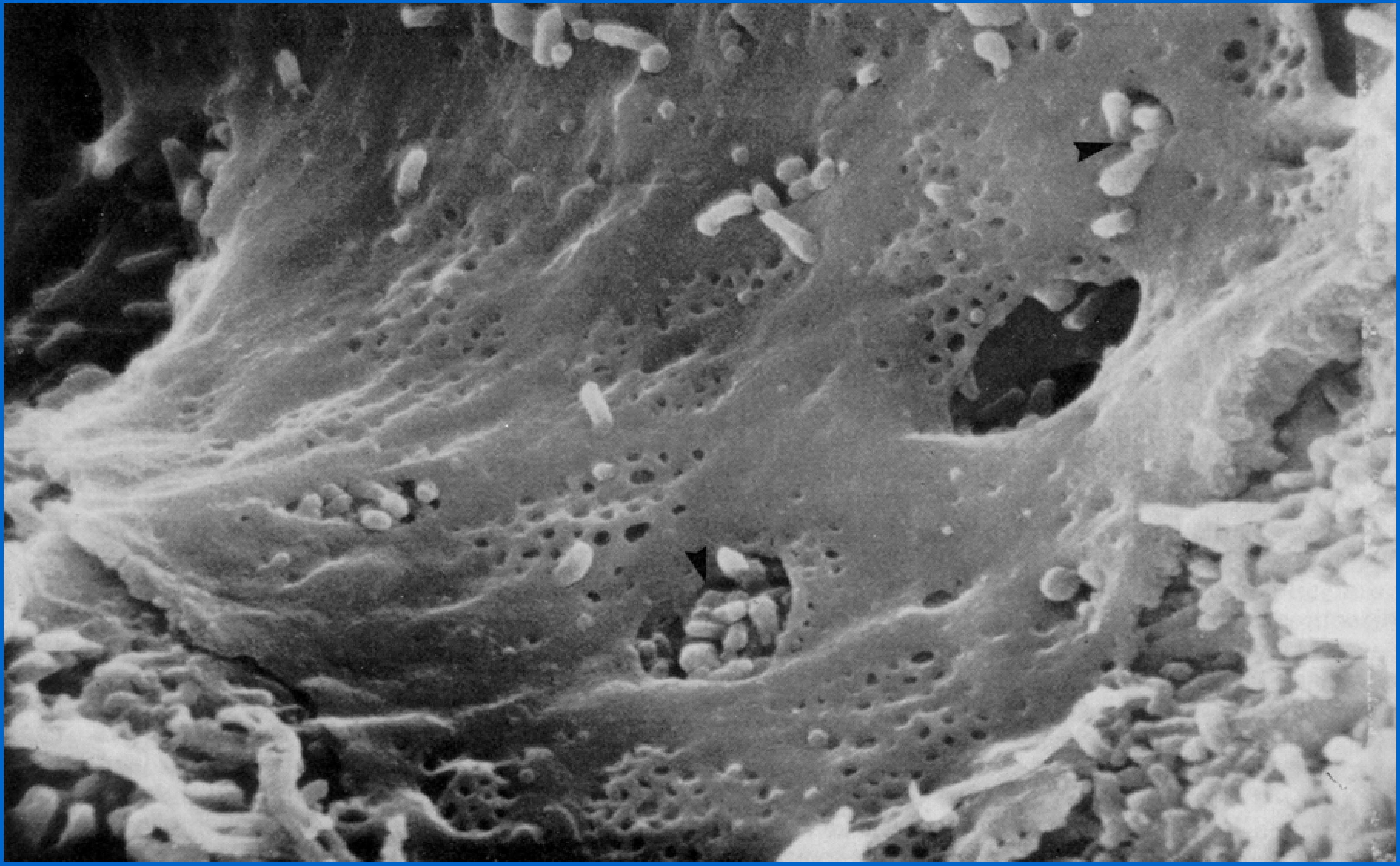


* From Atkinson AJ Jr, et al. Trends Pharmacol Sci 1991;12:96-101.

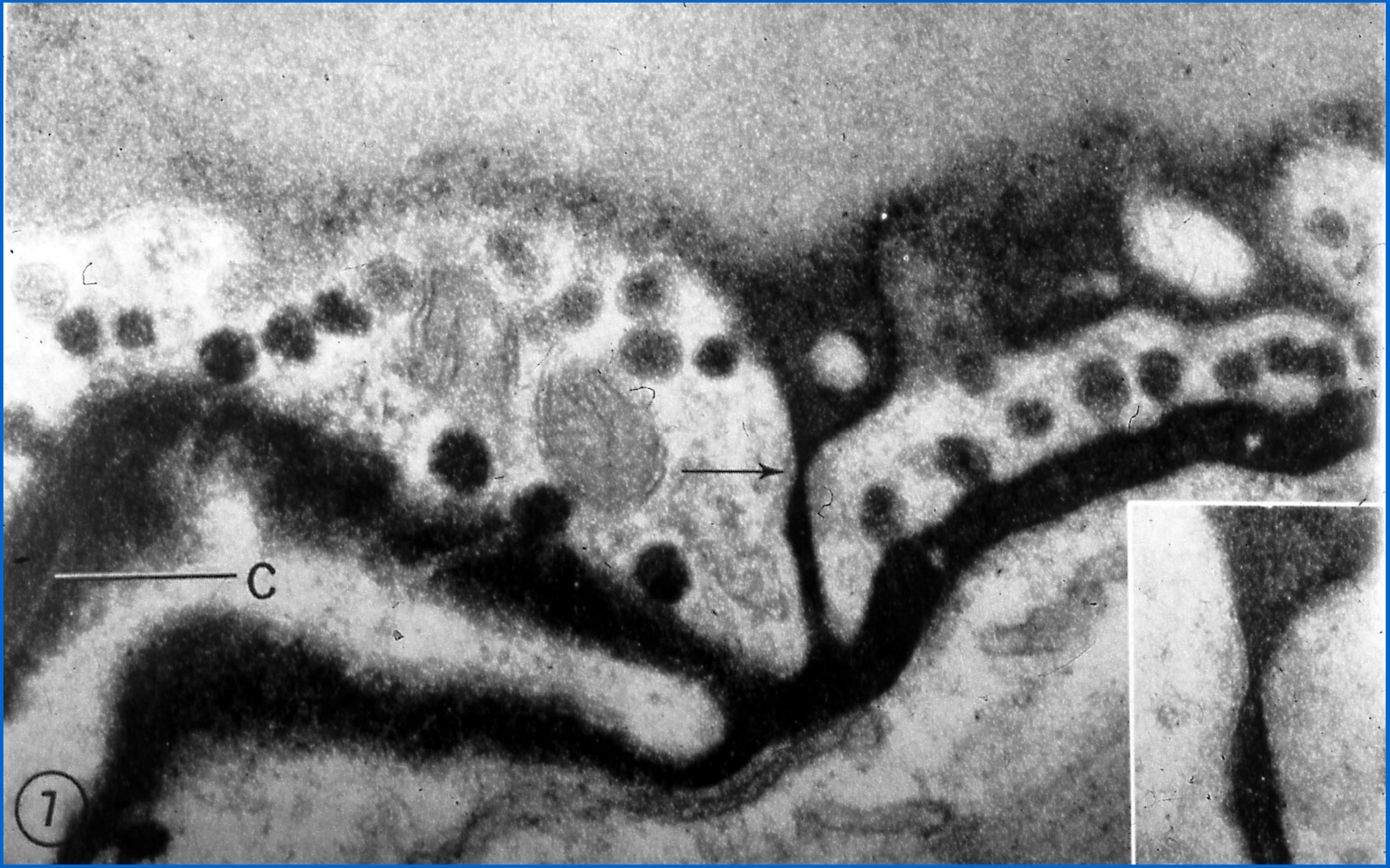
BASIS FOR KINETIC HETEROGENETIY OF INTERSTITIAL FLUID SPACE

EFFECTIVE PORE SIZE	CAPILLARY STRUCTURE	PRIMARY LOCATION
LARGE	FENESTRATED	SPLANCHNIC BED
SMALL	CONTINUOUS	SOMATIC TISSUES

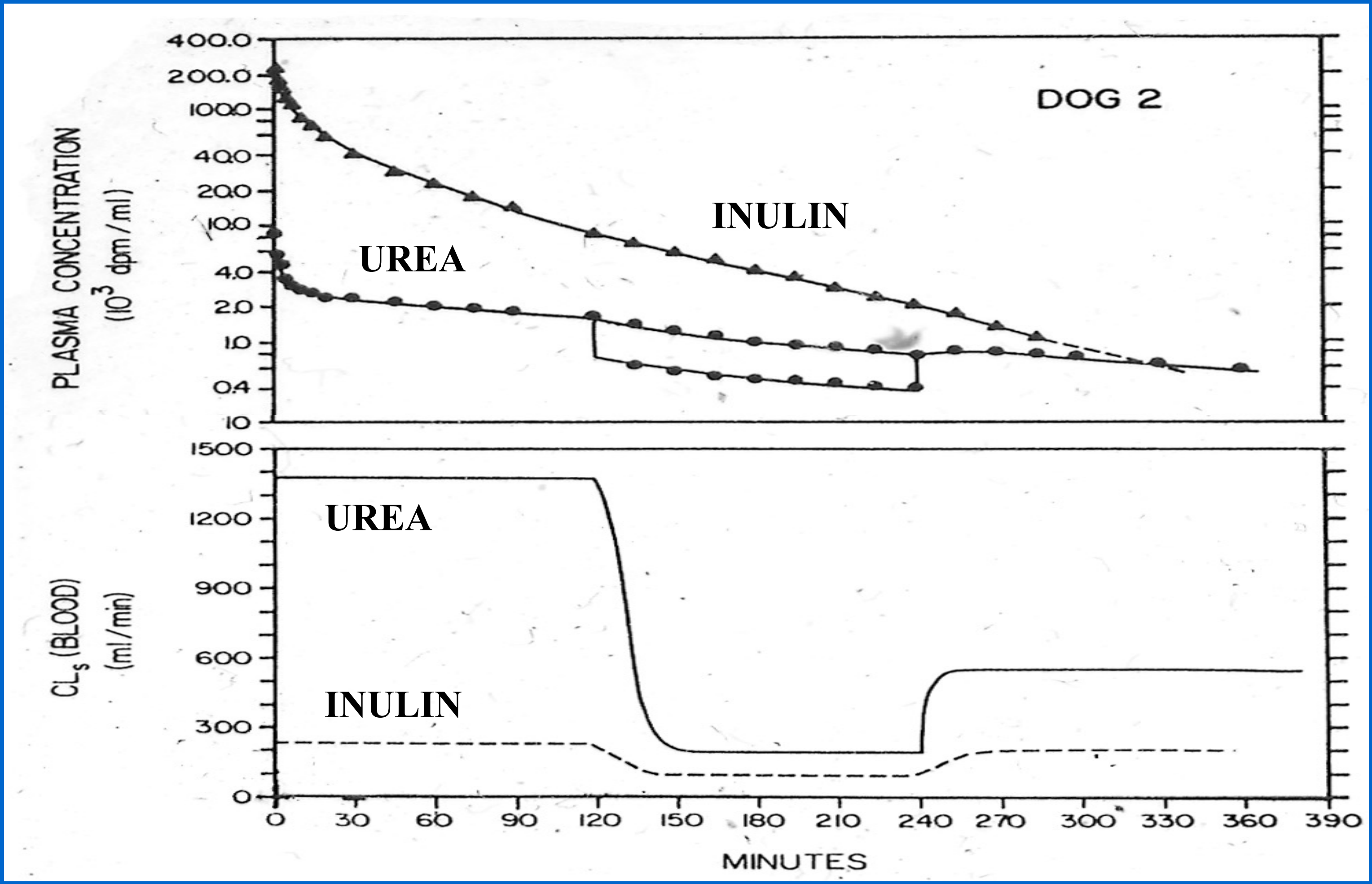
ENDOTHELIAL FENESTRAE IN HEPATIC SINUSOIDS



INTERENDOTHELIAL CELL JUNCTION IN CONTINUOUS CAPILLARY

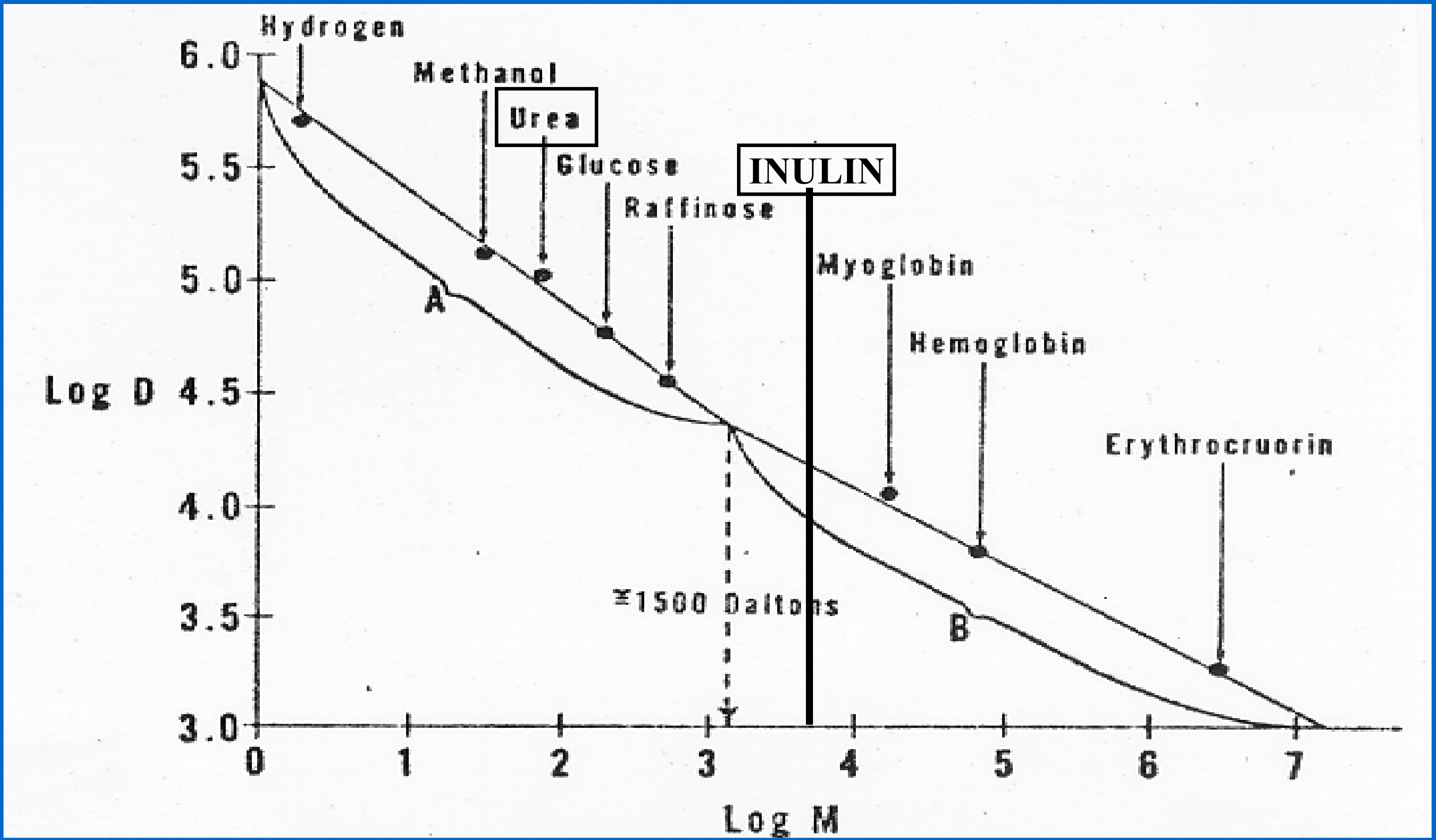


UREA (•) AND INULIN (▲) KINETICS DURING AND AFTER HEMODIALYSIS*



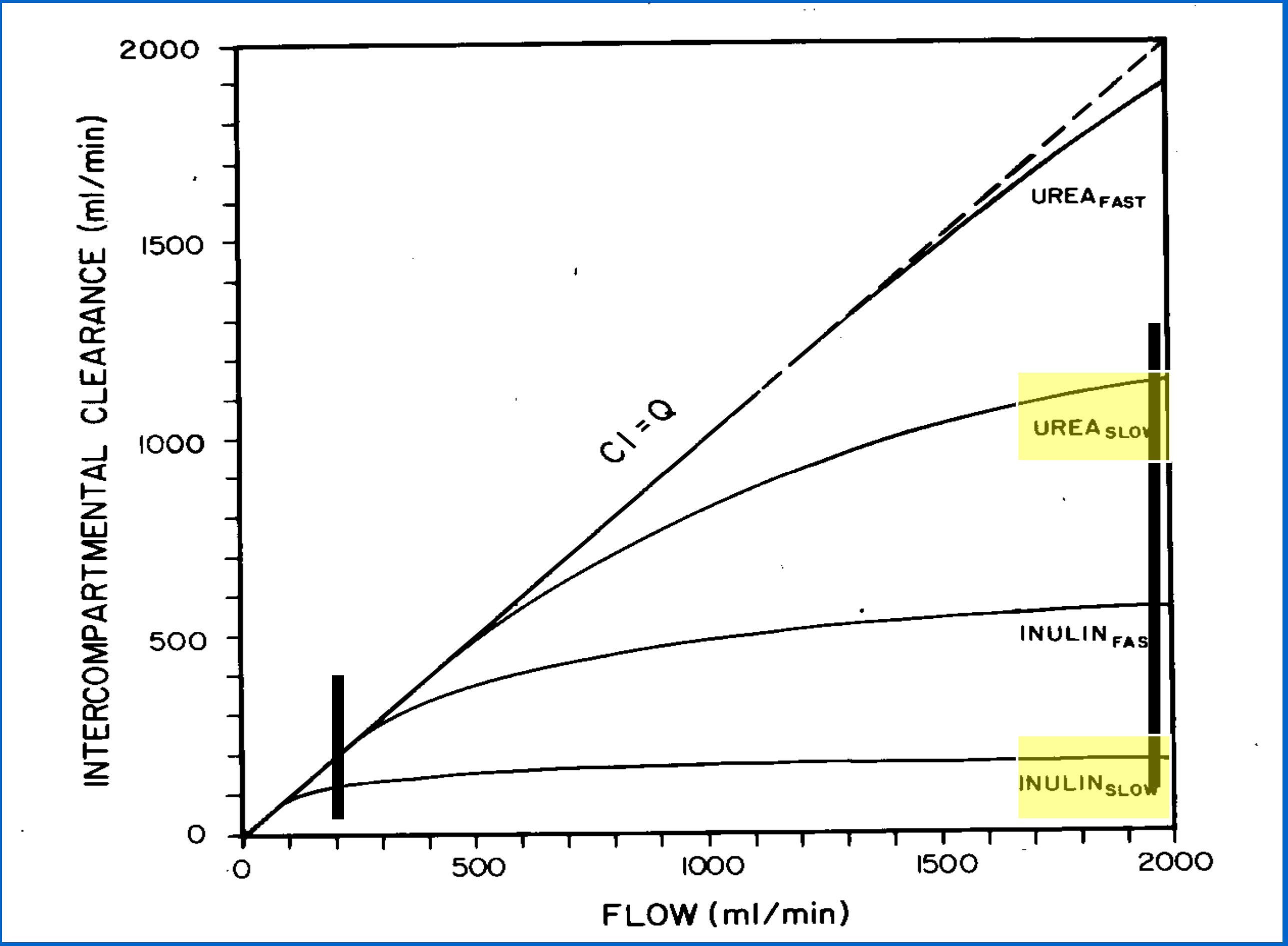
* From Bowsher DJ, et al. J Lab Clin Med 1985;105:489-97.

EFFECT OF MOLECULAR WEIGHT (M) ON SOLUTE DIFFUSIVITY (D)*



* From Henderson LW: *In*: Brenner BM, Rector FC Jr. The Kidney. 1976, p. 1643-71.

RELATIONSHIP BETWEEN BLOOD FLOW (Q) AND CL_I *



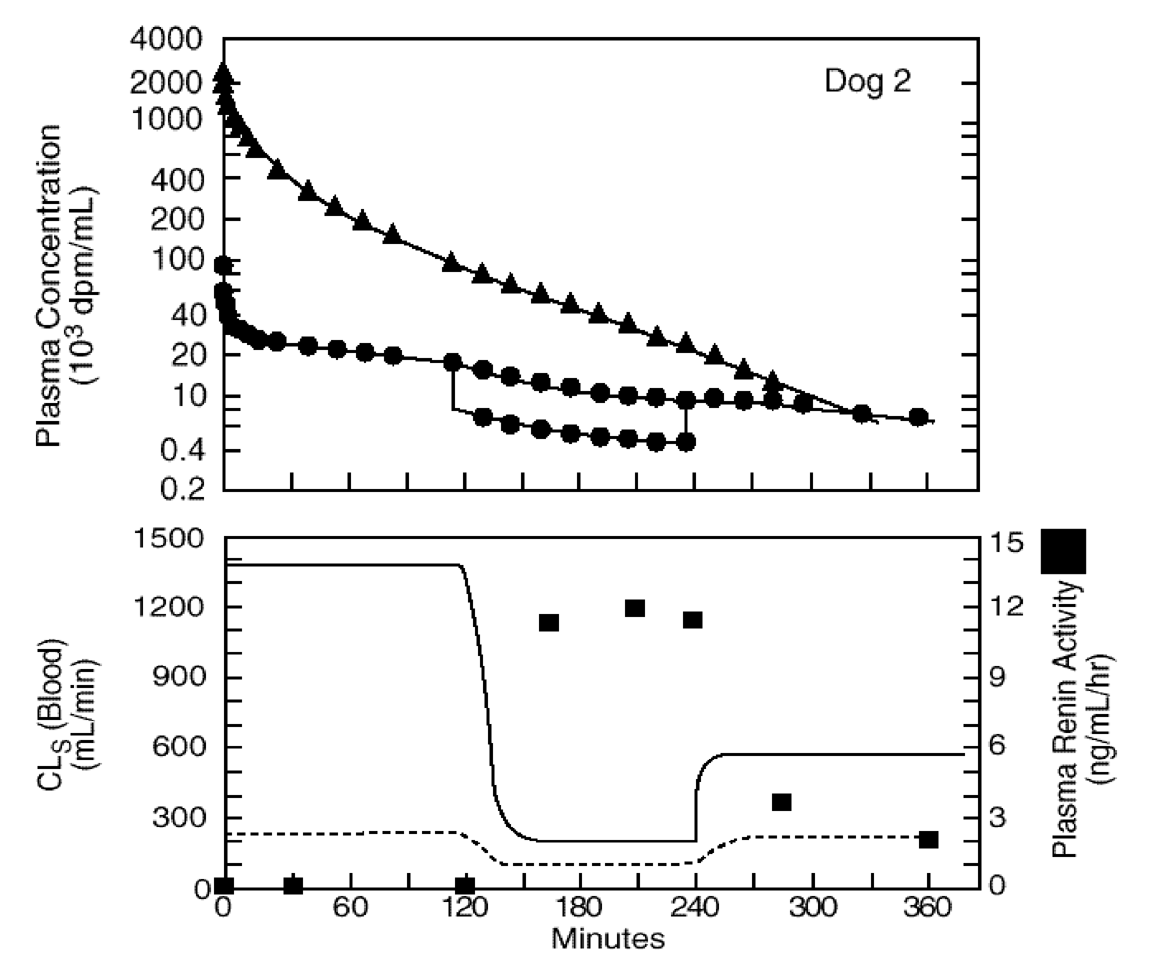
* From Bowsher DJ, et al. J Lab Clin Med 1985;105:489-97.

UREA AND INULIN KINETICS DURING AND AFTER HEMODIALYSIS

PARAMETER	BEFORE	DURING	AFTER
BLOOD FLOW			
Q_S (mL/min)	1991	199	405
Q_F (mL/min)	2332	2591*	2965*
C.O. (mL/min)	4399	2790	3370
PS			
INULIN (mL/min)	186	169	238
UREA (mL/min)	1649	1541	2164

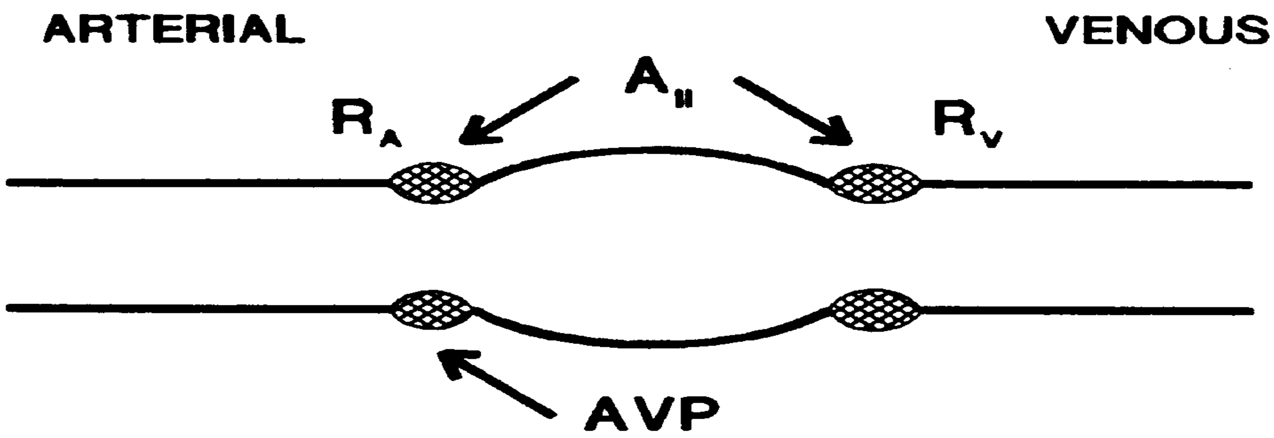
* ESTIMATED AS C.O. - Q_S

RENIN-ANGIOTENSIN SYSTEM ACTIVATION DURING AND AFTER HEMODIALYSIS*



* From Bowsher DJ, et al. J Lab Clin Med 1985;105:489-97.

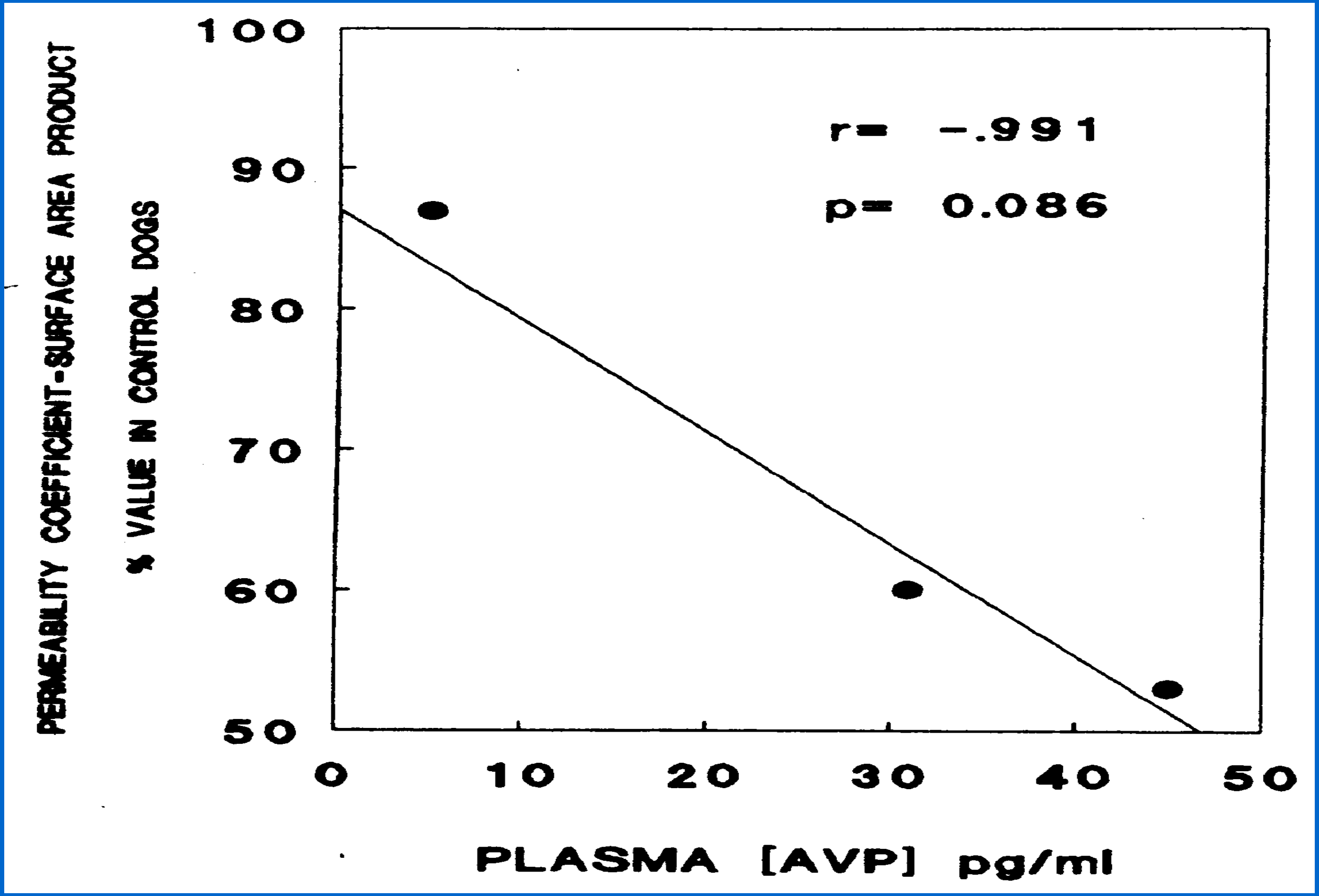
DIFFERENT MICROCIRCULATORY ACTIONS OF ANGIOTENSIN II AND AVP*



	R_A/R_V	P · S
A_{II}	↓	NORMAL
AVP	↑	↓

* From Atkinson AJ Jr: The Pharmacologist 1989;31:229-34.

EFFECT OF ARGININE VASOPRESSIN (AVP) ON P• S*



* From Atkinson AJ Jr: The Pharmacologist 1989;31:229-34.

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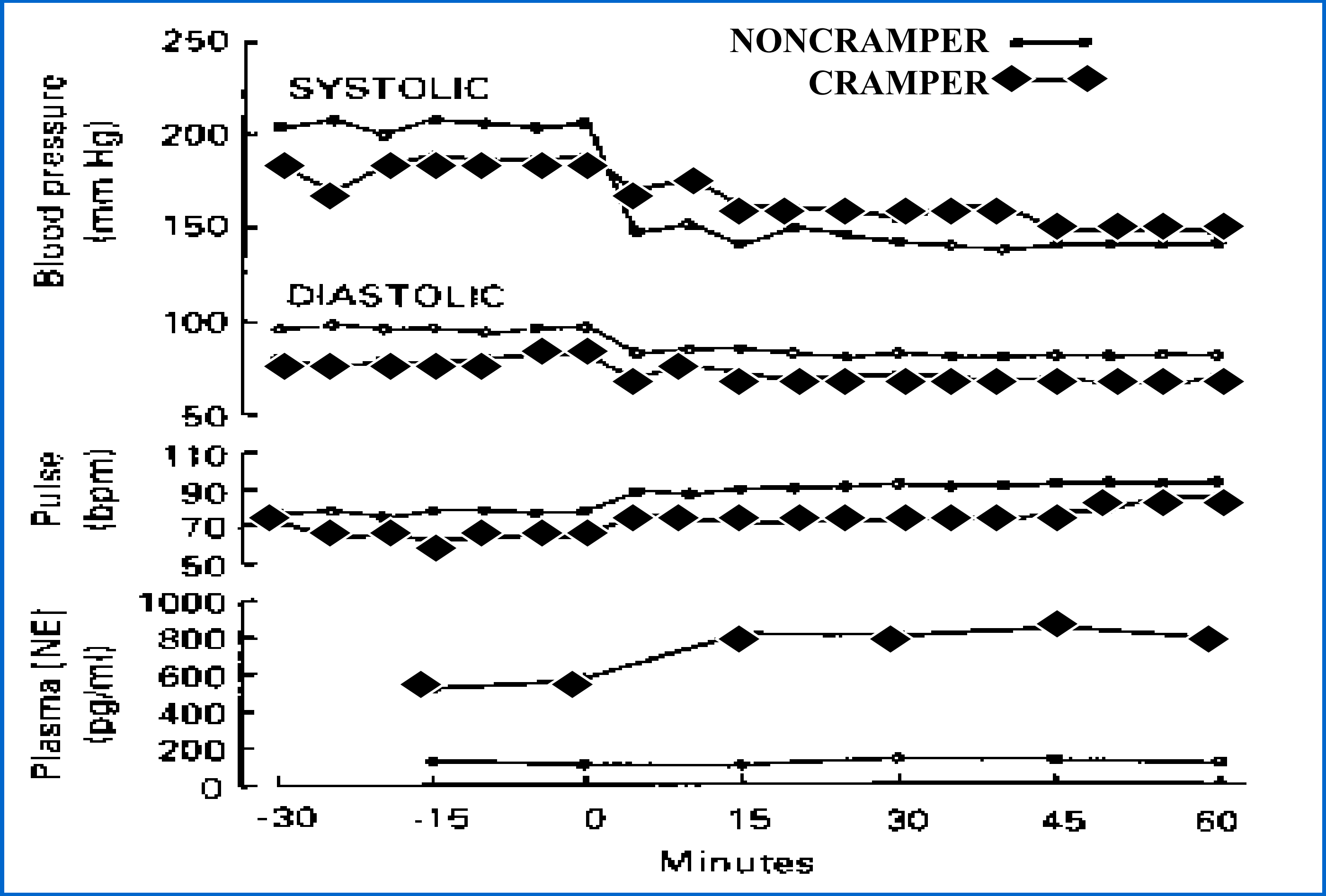
HEMODIALYSIS-ASSOCATED SKELETAL MUSCLE CRAMPS

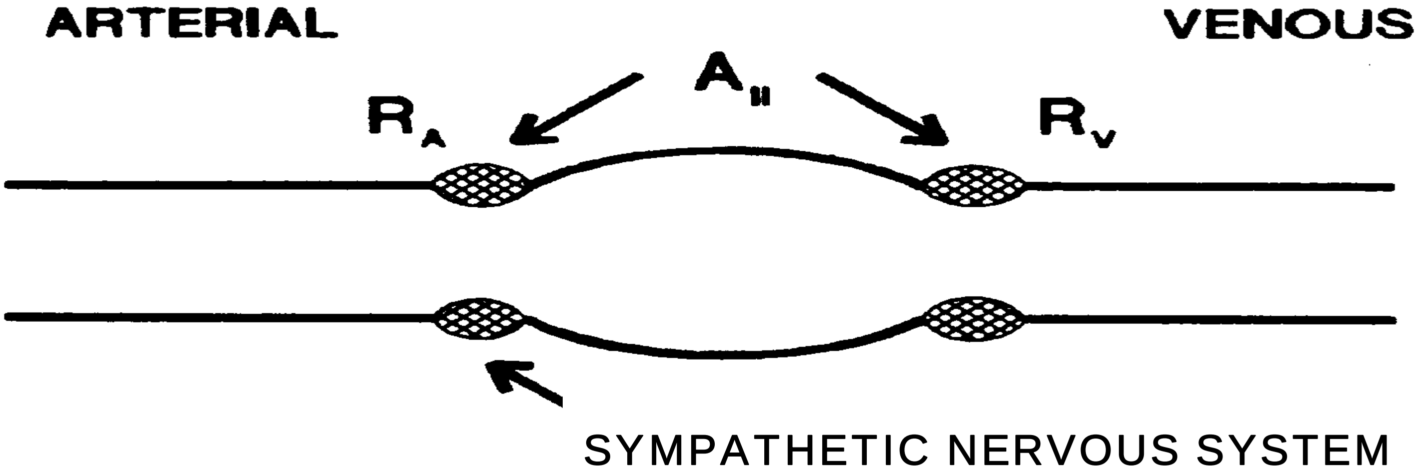
- COMPLICATE MORE THAN 20% OF HEMODIALYSIS SESSIONS
- OCCUR MORE FREQUENTLY IN SOME PATIENTS THAN OTHERS
- PATHOGENESIS UNCLEAR
- SYMPTOMATIC THERAPY: NaCl, MANNITOL
- PREVENTIVE THERAPY: NaCl INFUSION

RESPONSE OF CRAMPING AND NONCRAMPING PATIENTS TO TILT*



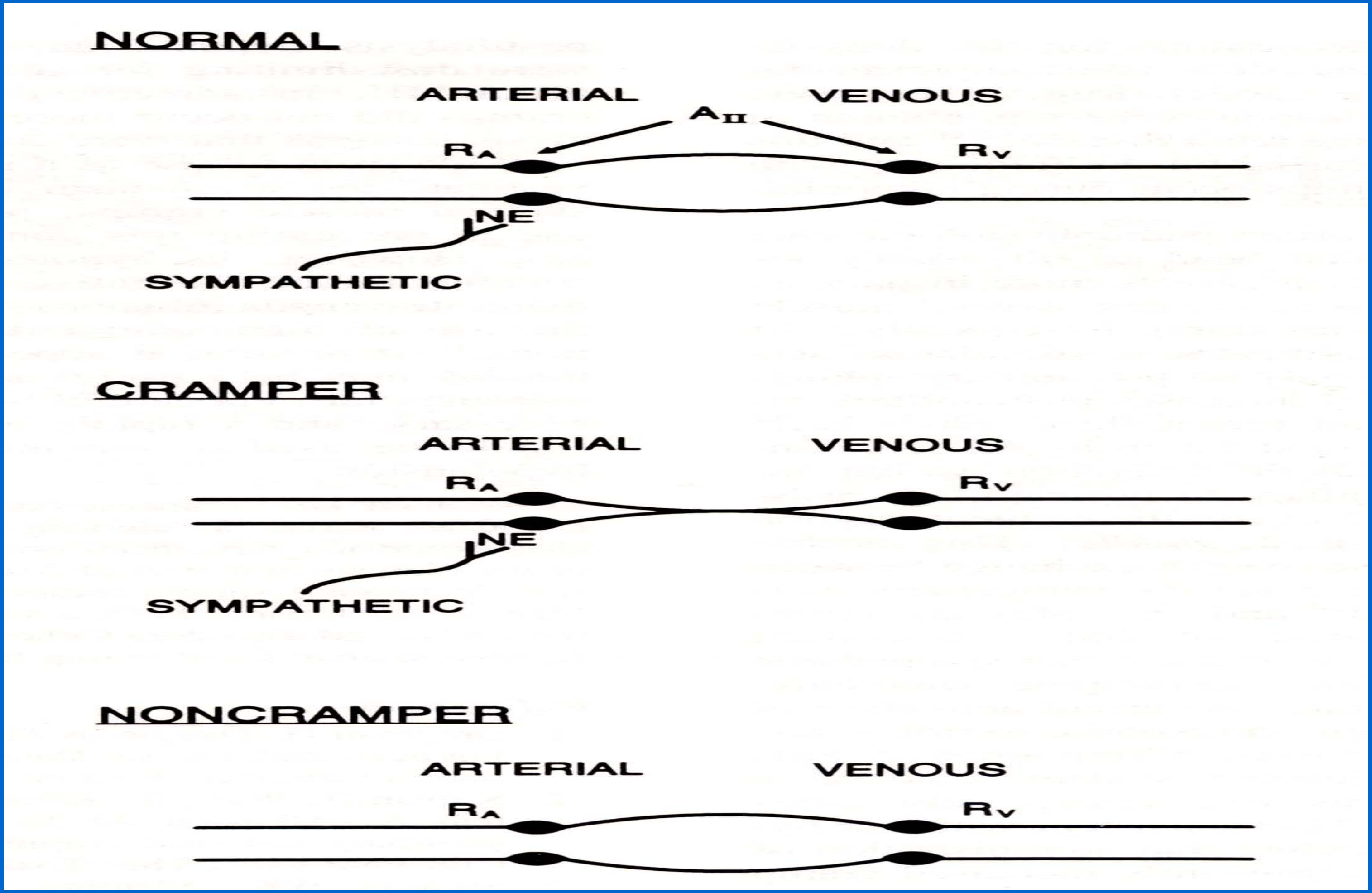
* Kaplan B et al.: Int J Clin Pharmacol Ther Toxicol 1992;30:173-80.

ACTIONS OF ANGIOTENSIN II & SYMPATHETIC NERVOUS SYSTEM



	R_A/R_V	P · S
A_{II}	↓	NORMAL
SYMPATHETIC NERVES	↑	↓

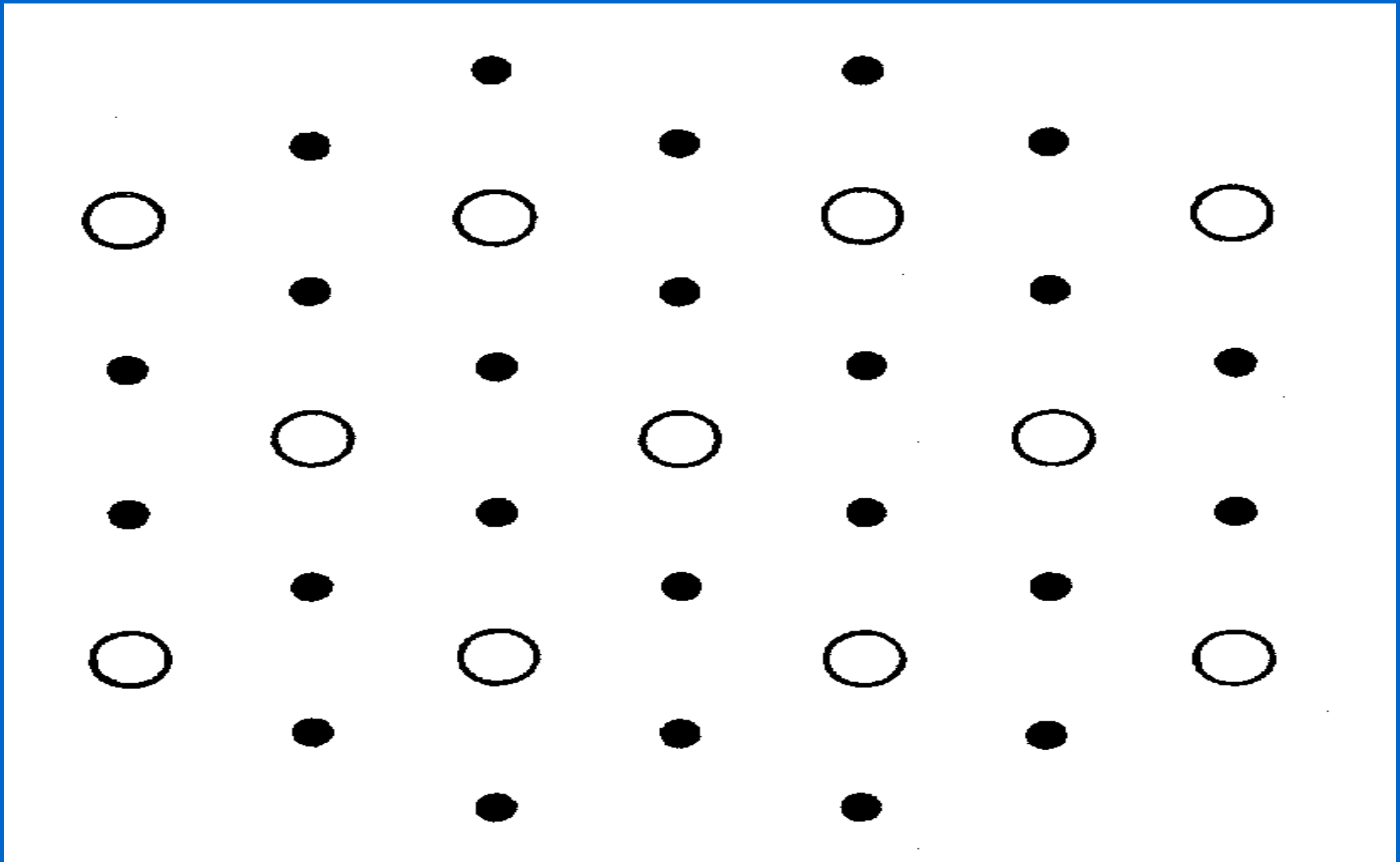
ONLY SOME PATIENTS HAVE DIALYSIS-ASSOCIATED SKELETAL MUSCLE CRAMPS*



* Sidhom OA, et al. Clin Pharmacol Ther 1994;56:445-51

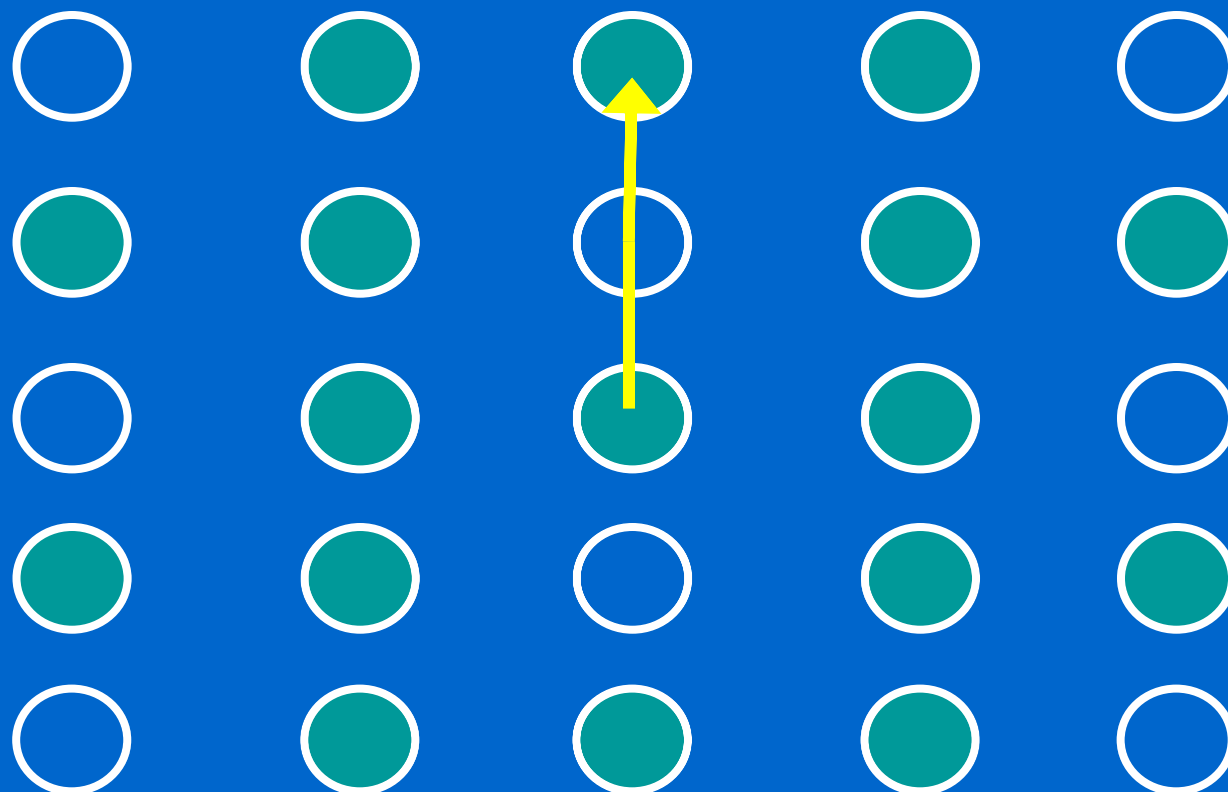
AUGUST KROGH
1920 NOBEL LAUREATE

CROSS SECTION OF MUSCLE SHOWING OPEN (O) & CLOSED (●) CAPILLARIES*



*From Krogh A. Nobel Lecture, December 11, 1920.

CAPILLARY DERECRUITMENT
(OPEN (O) & CLOSED (●) CAPILLARIES)



§ OPEN CAPILLARIES IN MUSCLE CROSS SECTION

PATHOGENESIS OF DIALYSIS-ASSOCIATED SKELETAL MUSCLE CRAMPS

HEMODIALYSIS

↓ X ← NaCl, MANNITOL

PLASMA VOLUME CONTRACTION

ACE INHIBITOR → +X ← PRAZOSIN

MODULATED SYMPATHETIC ACTIVATION

↓

PERIPHERAL VASOCONSTRICTION

↓

DERECRUITMENT OF MUSCLE CAPILLARIES

↓

IMPAIRED MUSCLE OXYGENATION

↓

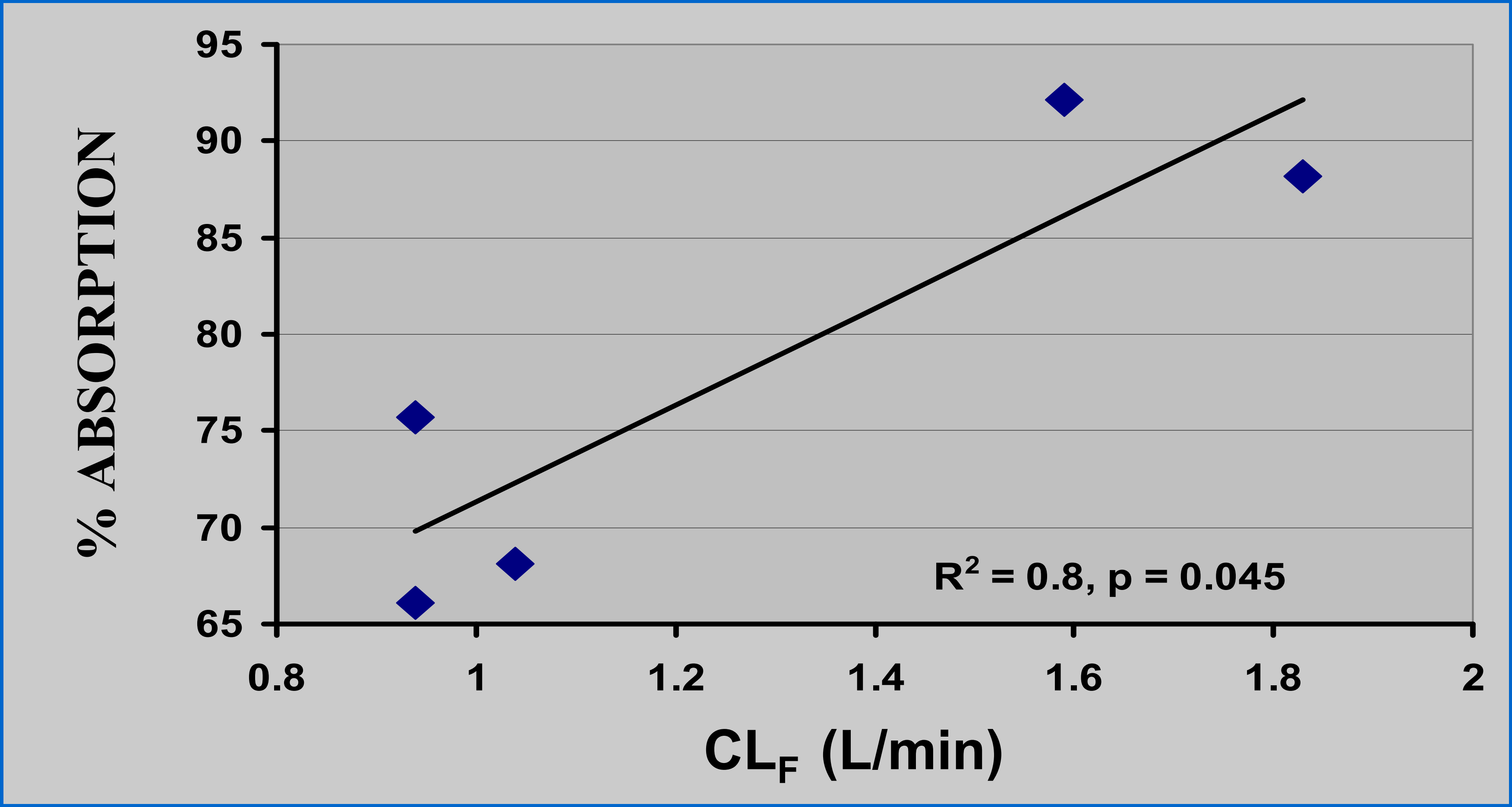
SKELETAL MUSCLE CRAMPS

CONCLUDING THOUGHT

ALTHOUGH NON-COMPARTMENTAL ANALYSIS OF PK DATA IS CURRENTLY IN VOGUE, IT IS UNABLE TO PROVIDE INSIGHT INTO SOME IMPORTANT PHENOMENA:

- IMPACT OF DIALYSIS-ASSOCIATED HEMODYNAMIC CHANGES (↓ CL_S)
- IMPACT OF ↓ SPLANCHNIC BLOOD FLOW (↓ CL_F) ON BIOAVAILABILITY

RELATIONSHIP BETWEEN CL_F AND EXTENT OF NAPA ABSORPTION*



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