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PHARMACOKINETICS IN PATIENTS REQUIRING RENAL REPLACEMENT Rx

PART 1: PK IN PATIENTS REQUIRING HEMODIALYSIS

October 22, 2009



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Pharmacology and Biochemistry**

Feinberg School of Medicine

Northwestern University . . .

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JOHN JACOB ABEL

1857 - 1938



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

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

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



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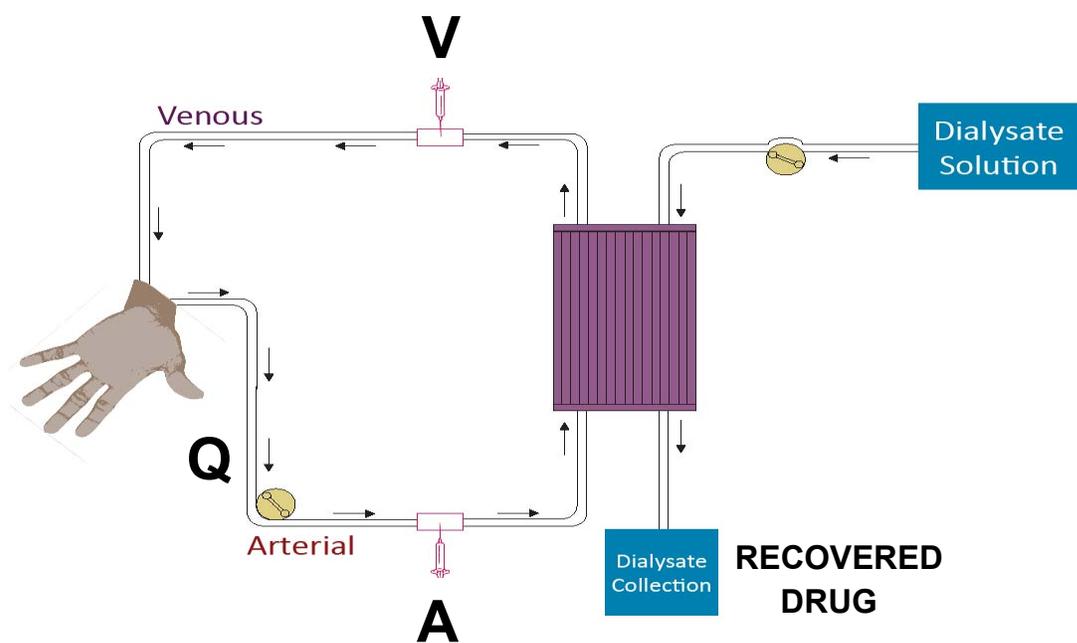
ELIMINATION BY DIFFERENT ROUTES

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

*not actually measured in routine PK studies

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DATA SOURCES FOR FICK EQUATION



⋮

IMPACT OF CL_D

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

⋮

⋮

CRITERION FOR DIALYSIS EFFICACY*

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

**BUT CLEARANCE ESTIMATES
MUST BE COMPARABLE**

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

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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

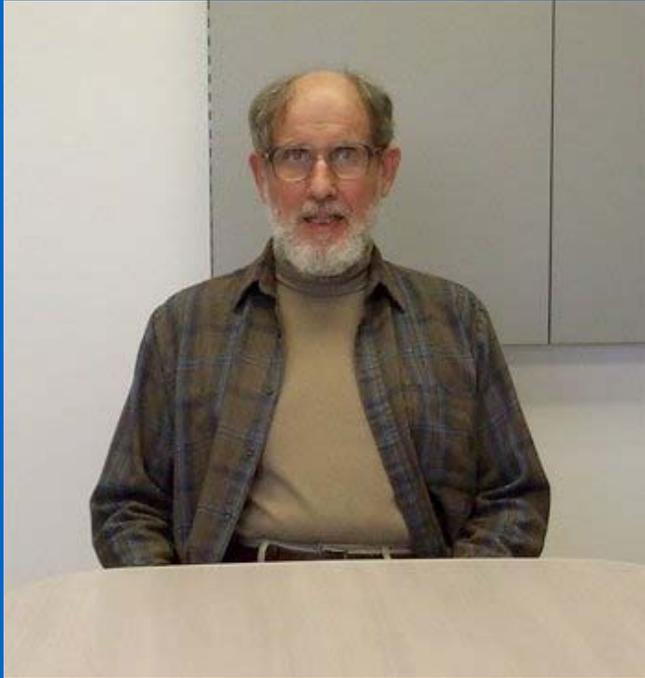
USE OF KINETIC METHODS FOR ANALYSIS

PATHOPHYSIOLOGIC CONSEQUENCES

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**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

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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**
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DIALYZER PERMEABILITY VS. FREE WATER DIFFUSION COEFFICIENTS

PROCAINAMIDE/NAPA:

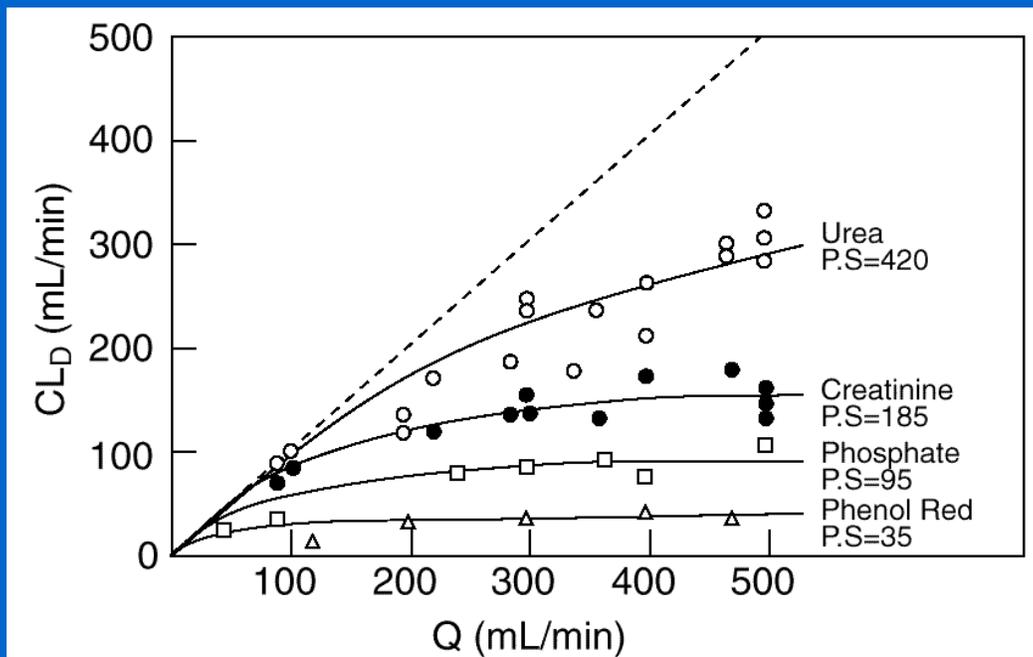
RATIO OF DIALYZER PERMEABILITY COEFFICIENTS* 1.28 ± 0.23

RATIO OF FREE WATER DIFFUSION COEFFICIENTS 1.23

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

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DIALYSIS CLEARANCE VS. DIALYZER BLOOD FLOW*



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

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POSSIBLE USE FOR INTRA-DIALYZER TRANSFER OF RESULTS

- PERFORM PRELIMINARY *IN VITRO* STUDY TO OBTAIN P RATIO FOR DRUG & STANDARD COMPOUND FOR DIALYZER BEING USED IN DIALYSIS STUDY (RECORD Q & RBC/PLASMA).
- THIS RATIO CAN BE USED TO ESTIMATE DRUG CL_D FOR OTHER DIALYZERS AND OTHER Q VALUES IF P OF STANDARD COMPOUND FOR THAT DIALYZER IS KNOWN.
- **NEED TO SELECT APPROPRIATE STANDARD COMPOUND (? CREATININE).**

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USE OF KINETIC METHODS FOR ANALYSIS
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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:

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

Fick Equation:

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

In Each Case:

$$CL = Q \cdot E$$

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

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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

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PLASMA VS. BLOOD CLEARANCE

RECOVERY : $CL_P = \frac{U \cdot V}{P}$ $CL_B = \frac{U \cdot V}{B}$

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

IF $B > P$: $CL_P > CL_B$, 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 :

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

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GOALS OF DIALYSIS DISCUSSION

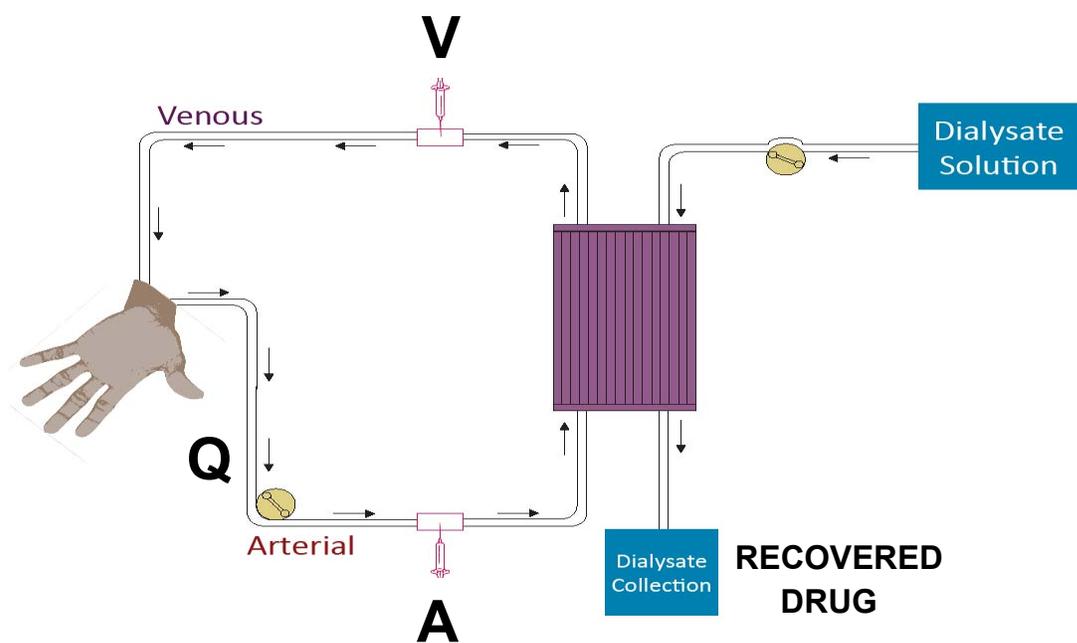
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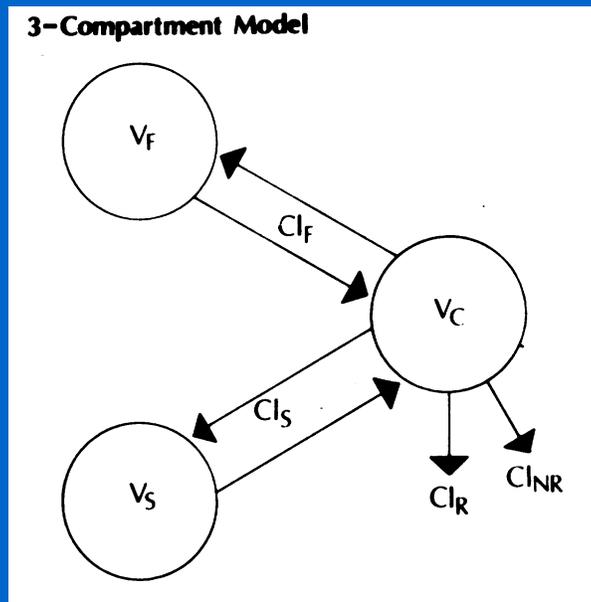
PHYSIOLOGIC CHANGES DURING DIALYSIS
USE OF KINETIC METHODS FOR ANALYSIS
PATHOPHYSIOLOGIC CONSEQUENCES

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DATA SOURCES FOR FICK EQUATION

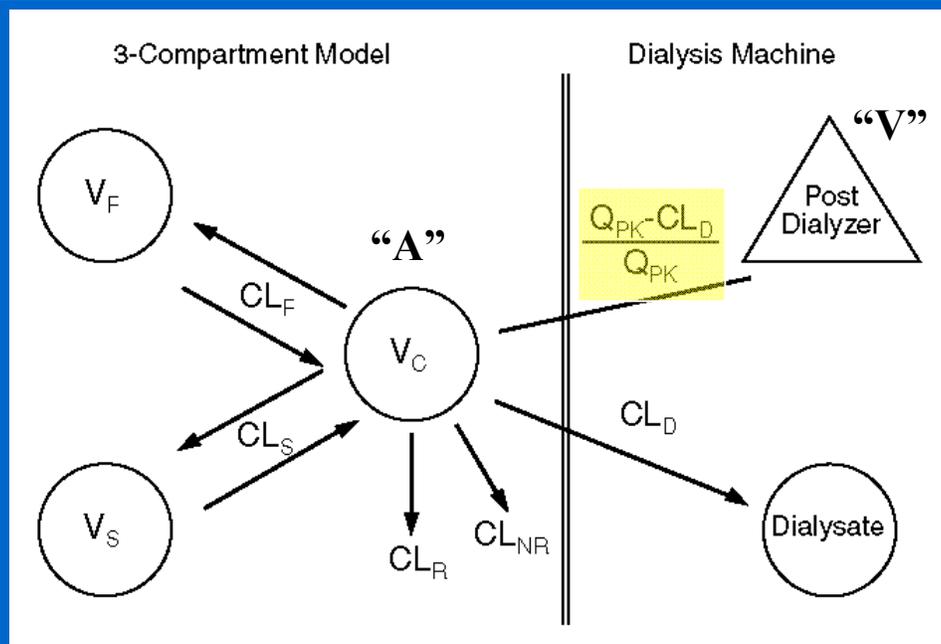


KINETIC MODEL USED TO ANALYZE HEMODIALYSIS DATA*



* 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

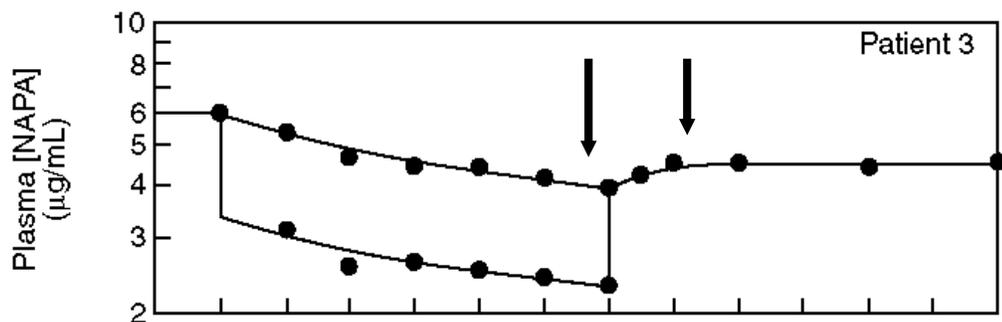
$$CL = Q \left[\frac{A - V}{A} \right]$$

$$CLA = QA - QV$$

$$QV = QA - CLA$$

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

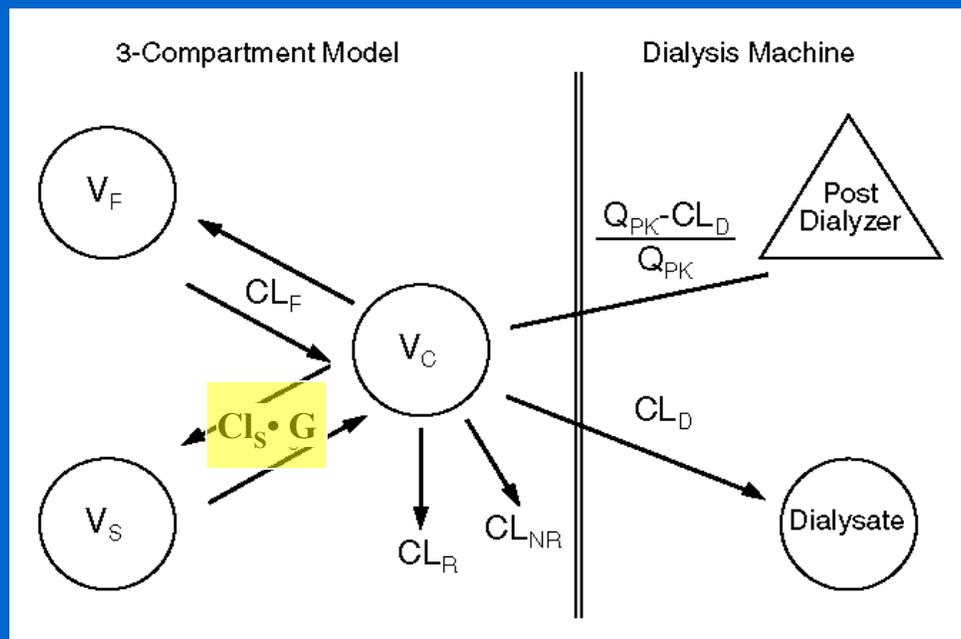
TWO PROBLEMS WITH FIXED-PARAMETER MODEL*



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

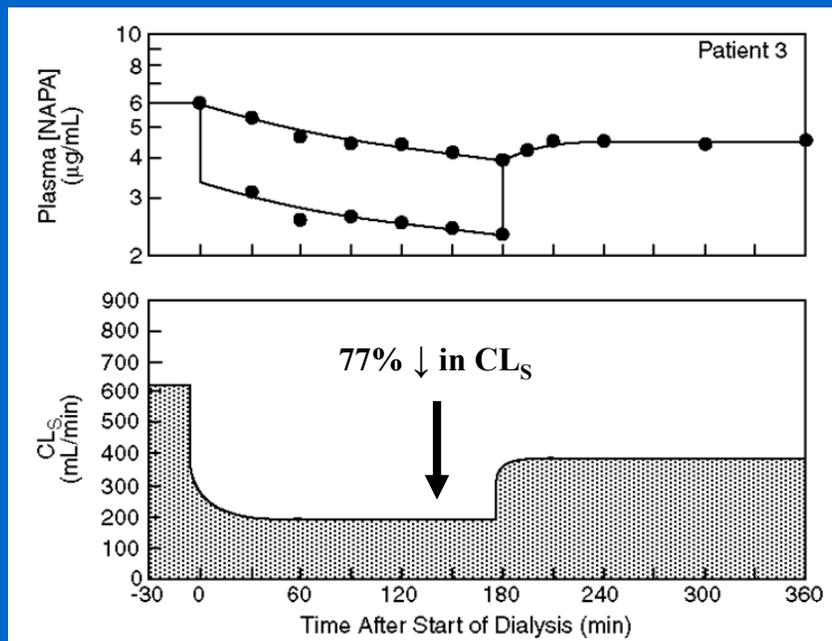
* From Stec GP, et al. Clin Pharmacol Ther 1979;26:618-28.

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.

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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.

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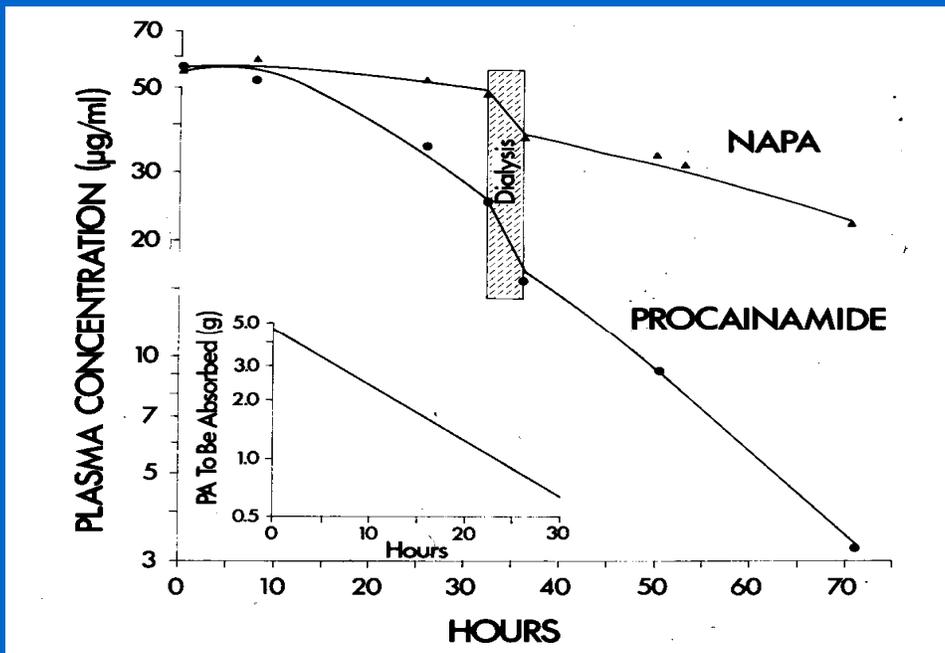
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DIALYSIS CASE HISTORY (cont.)

Fifteen hours after dialysis, PA and NAPA levels were 9.2 $\mu\text{g}/\text{mL}$ and 33 $\mu\text{g}/\text{mL}$, respectively. The patient had returned to normal sinus rhythm with QRS = 0.12 sec.

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KINETIC ANALYSIS OF HEMODIALYSIS FOR PROCAINAMIDE TOXICITY*



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

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CRITERION FOR DIALYSIS EFFICACY*

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

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

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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 SUBSTANTIALY**

PA: 25.7 µg/mL → 15.5 µg/mL

NAPA: 47.0 µg/mL → 35.5 µg/mL

AND PATIENT'S CONDITION STABILIZED

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PA & NAPA KINETICS IN TOXIC PATIENT

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

ESTIMATION OF V_d

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

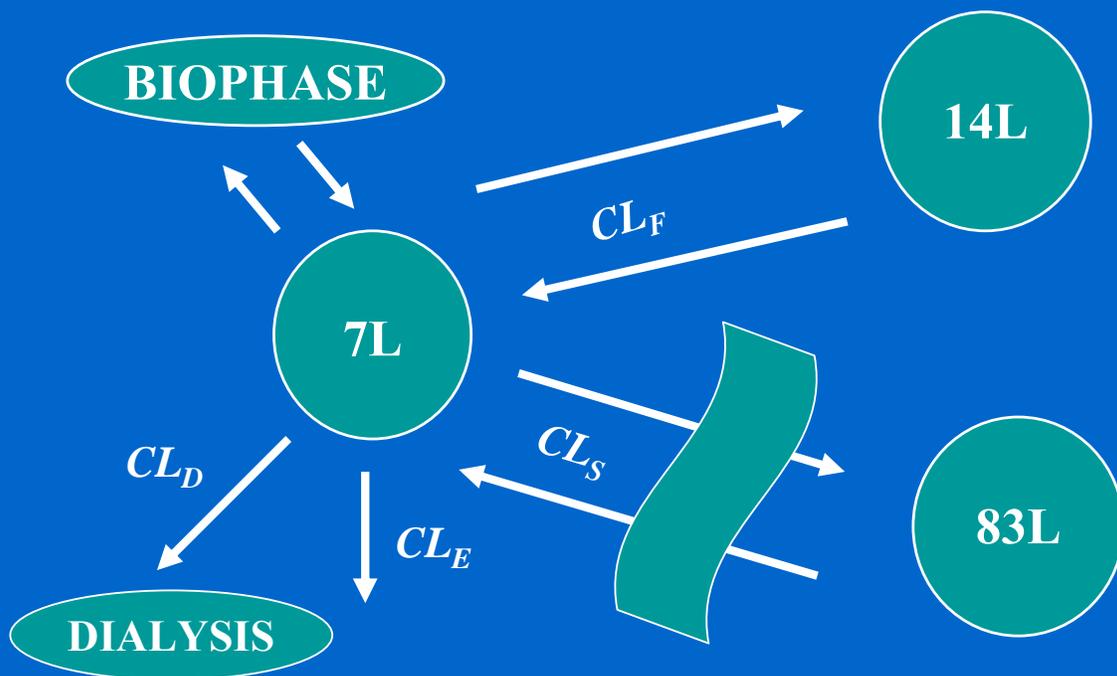
USUAL V_d ESTIMATE :

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

DIALYSIS V_d ESTIMATE :

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

SEQUESTRATION OF DRUG IN SOMATIC TISSUES



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EFFICACY OF EXTRACORPOREAL TREATMENT OF DRUG TOXICITY

- TOTAL EXTENT OF DRUG REMOVAL MAY BE COMPROMIZED BY \downarrow CL_S .
 - \downarrow CL_S FROM SOMATIC TISSUES CAN ACCELERATE \downarrow IN DRUG CONCENTRATION TO WHICH VITAL ORGANS (CNS, HEART) ARE EXPOSED AND RESULT IN A BENEFICIAL CLINICAL RESPONSE $>$ EXTENT OF DRUG REMOVAL.
 - \downarrow 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 $P \cdot S$ PRODUCT DECREASES

BOTH DECREASE

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RENKIN EQUATION*

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

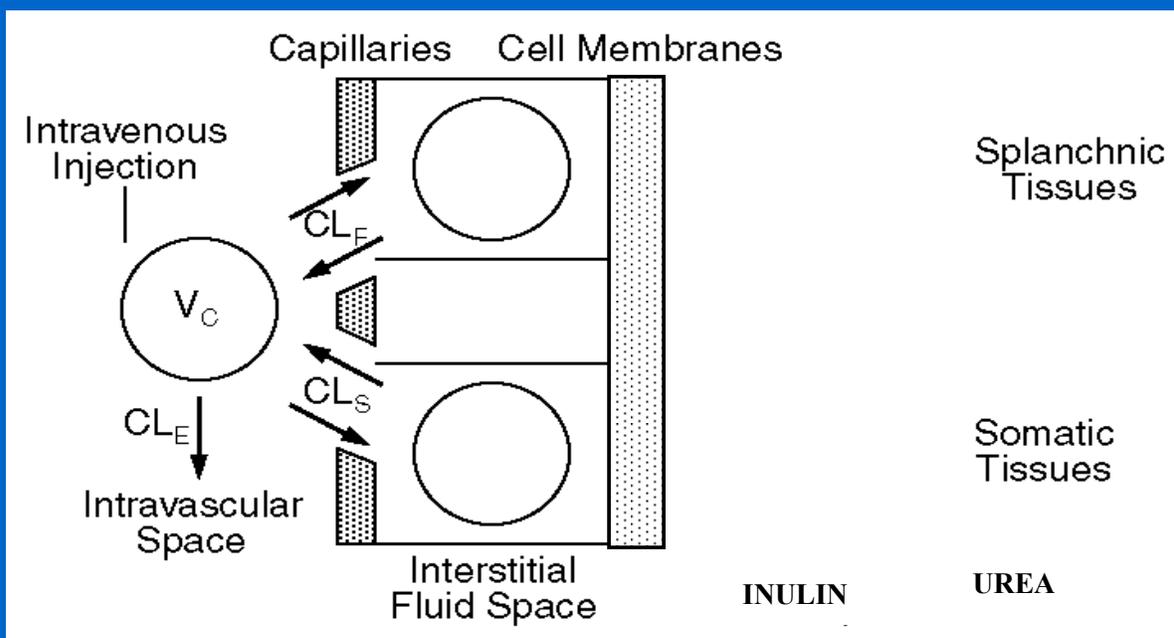
Q = capillary blood flow

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

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

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MULTICOMPARTMENTAL MODEL OF INULIN AND UREA KINETICS*



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

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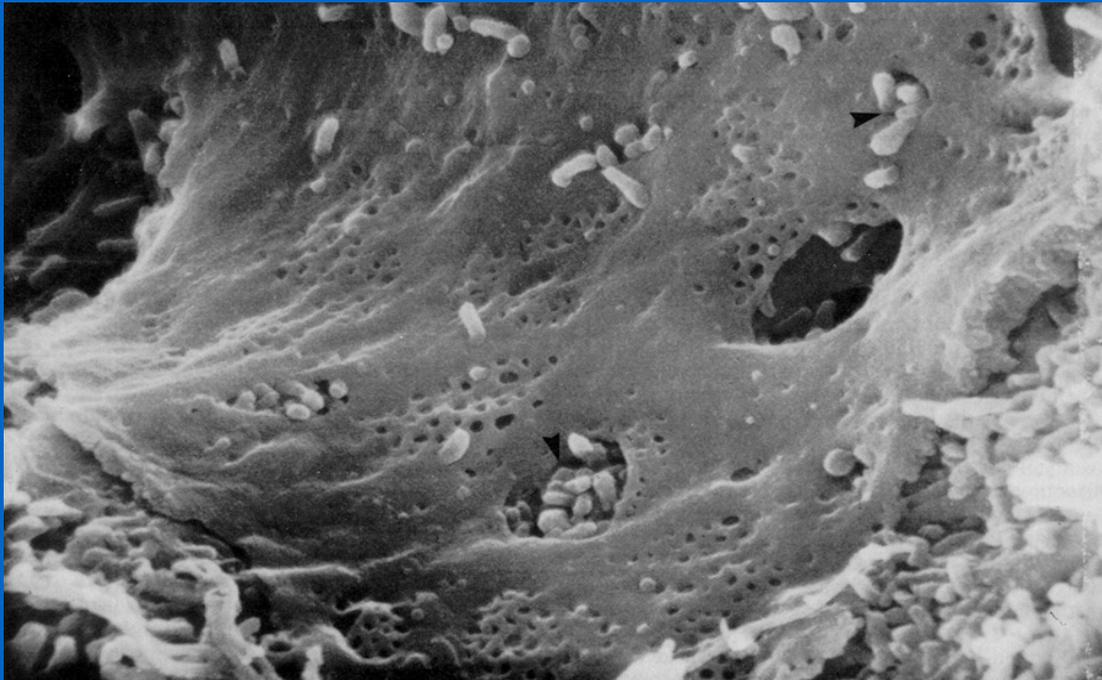
BASIS FOR KINETIC HETEROGENETIY OF INTERSTITIAL FLUID SPACE

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

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ENDOTHELIAL FENESTRAE IN HEPATIC SINUSOIDS

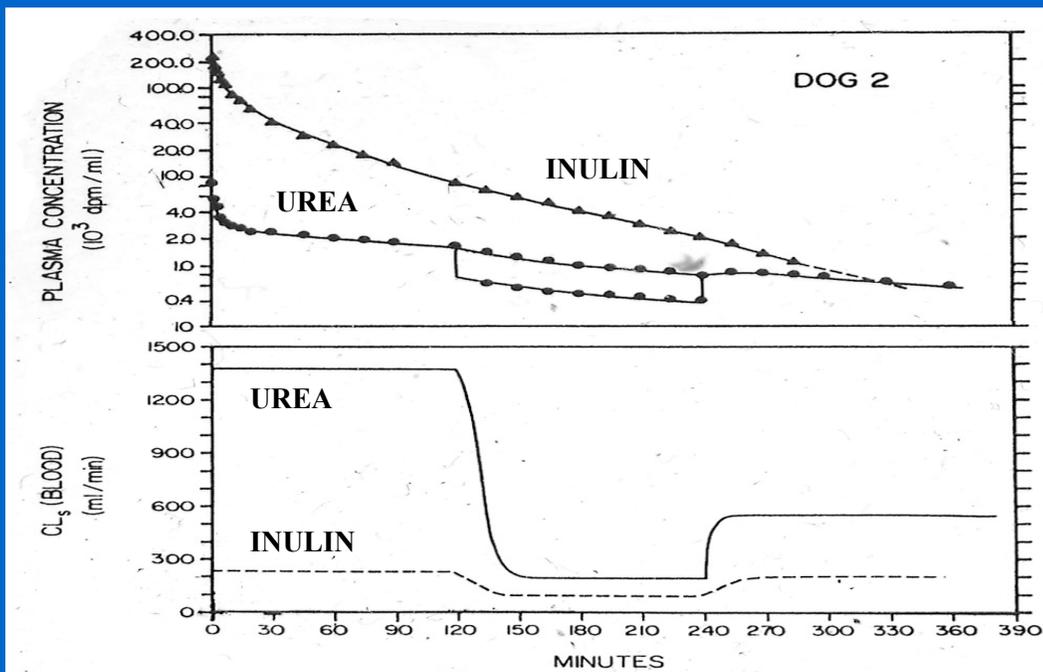


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INTERENDOTHELIAL CELL JUNCTION IN CONTINUOUS CAPILLARY

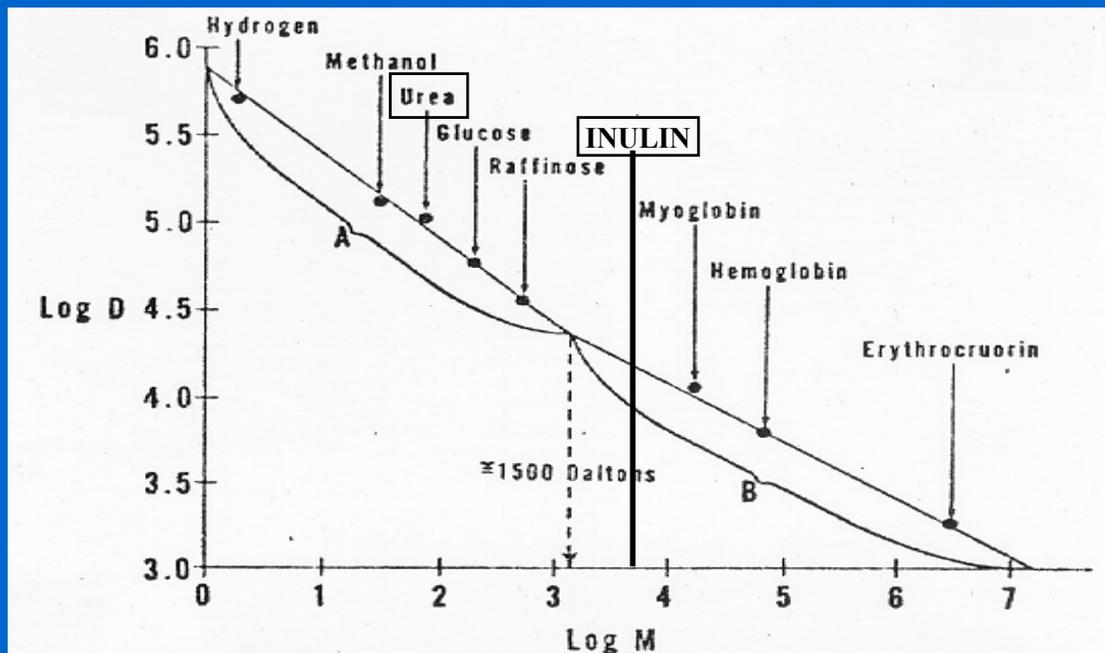


UREA (●) AND INULIN (▲) KINETICS DURING AND AFTER HEMODIALYSIS*



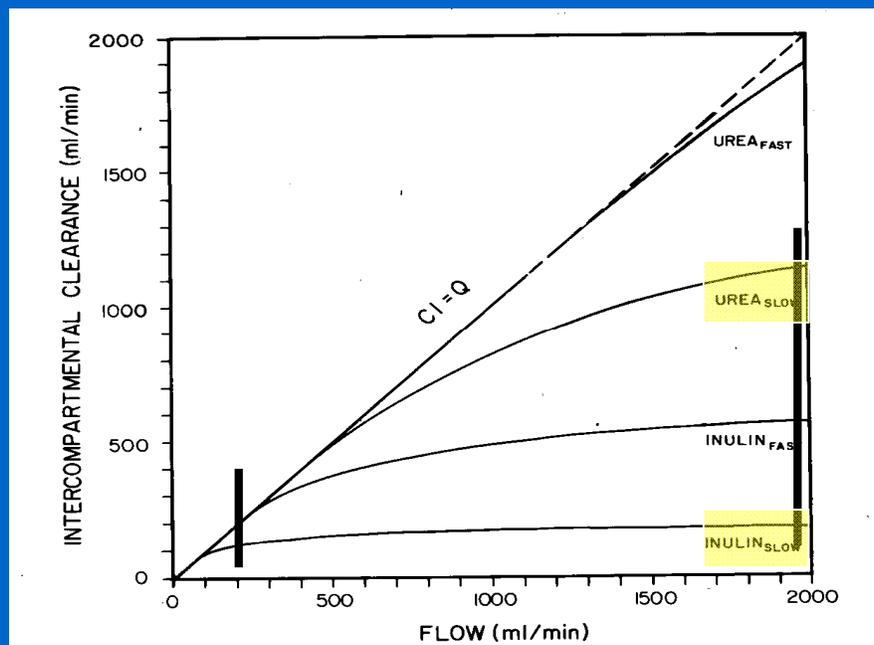
* From Bowsher DJ, et al. J Lab Clin Med 1985;105:489-97.

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 *



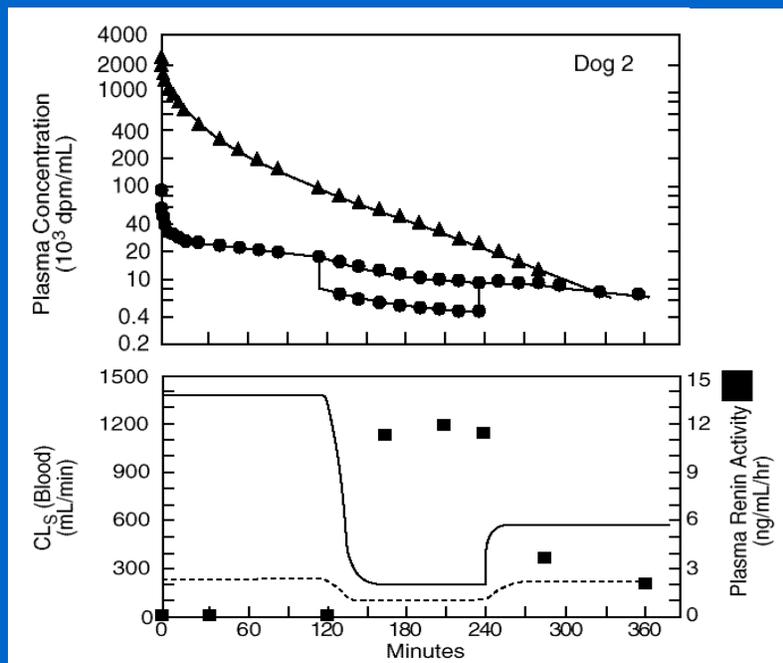
* From Bowsher DJ, et al. J Lab Clin Med 1985;105:489-97.

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

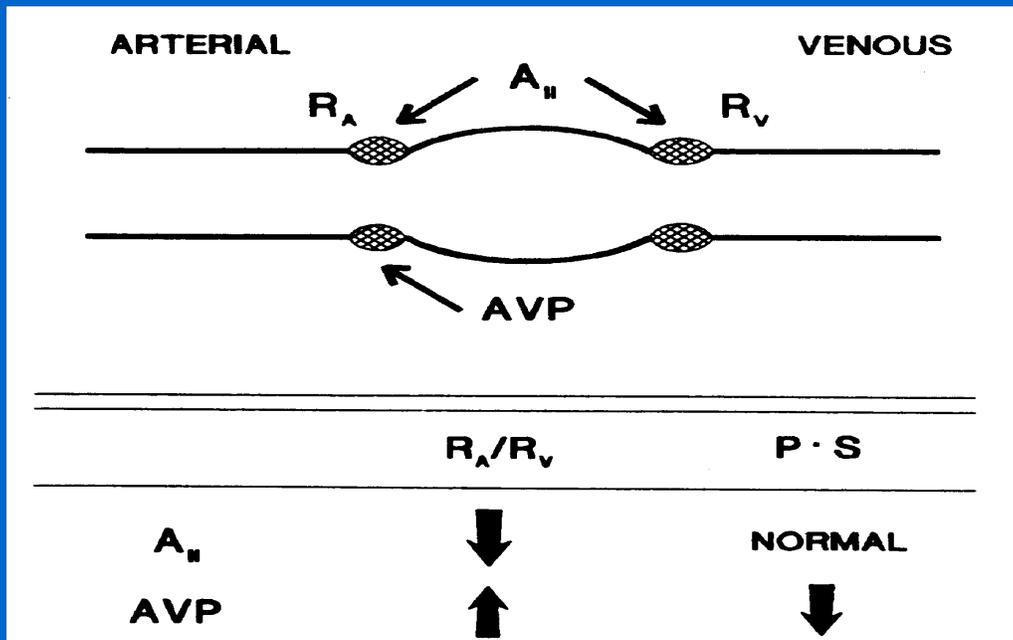
* ESTIMATED AS C.O. - Q_S

RENIN-ANGIOTENSIN SYSTEM ACTIVATION DURING AND AFTER HEMODIALYSIS*



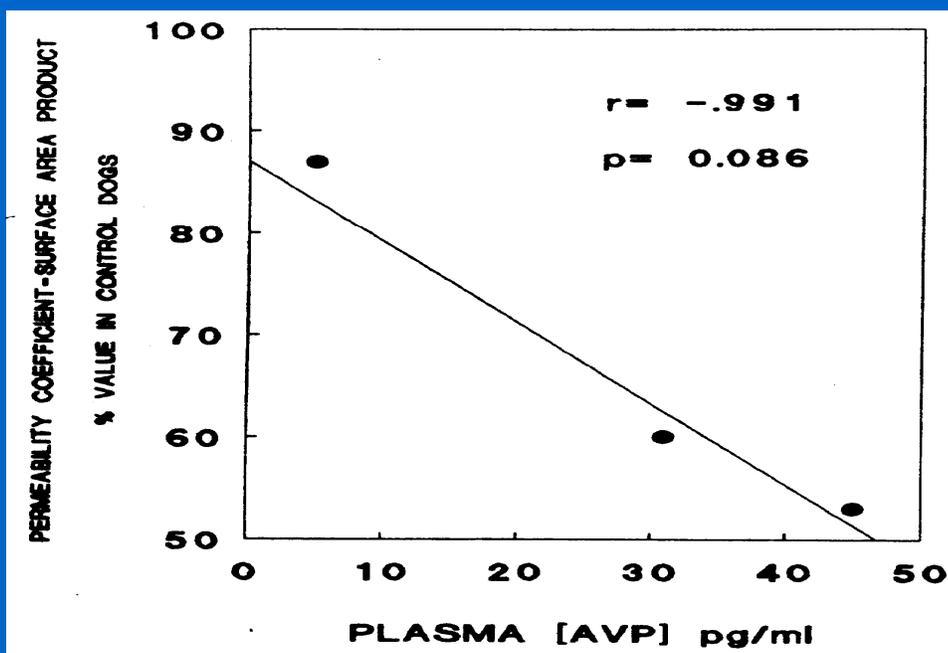
* From Bowsher DJ, et al. J Lab Clin Med 1985;105:489-97.

DIFFERENT MICROCIRCULATORY ACTIONS OF ANGIOTENSIN II AND AVP*



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

EFFECT OF ARGININE VASOPRESSIN (AVP) ON $P \cdot S^*$



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

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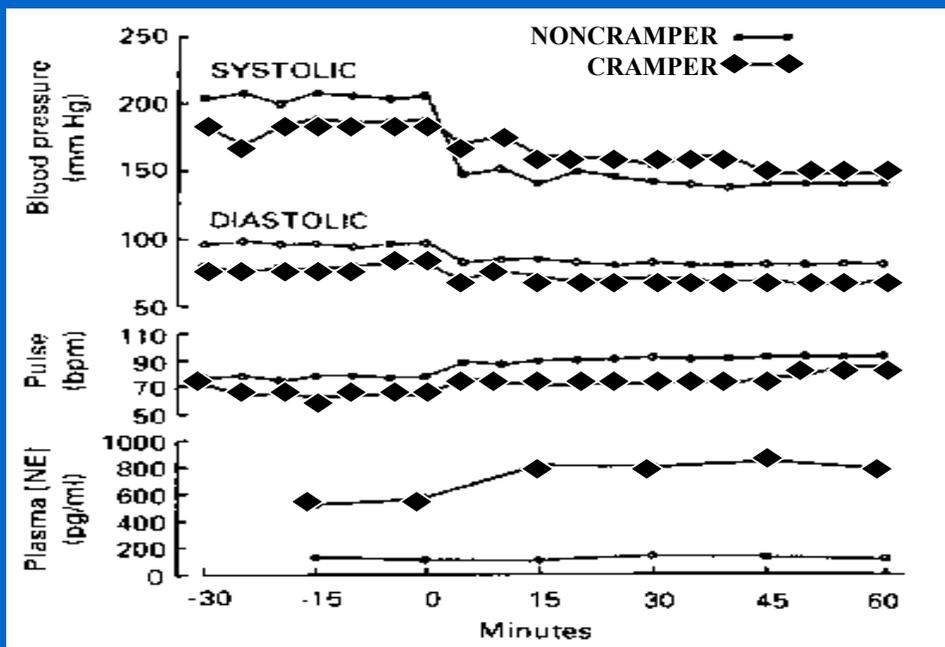
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HEMODIALYSIS-ASSOCIATED SKELETAL MUSCLE CRAMPS

- **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**

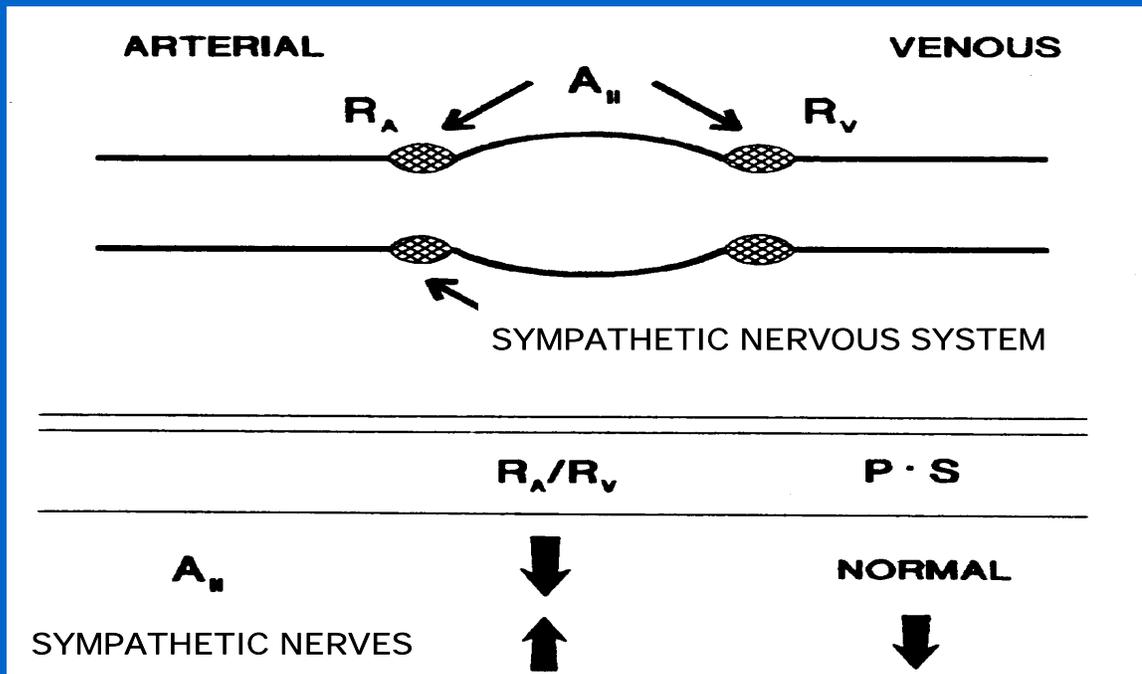
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RESPONSE OF CRAMPING AND NONCRAMPING PATIENTS TO TILT*

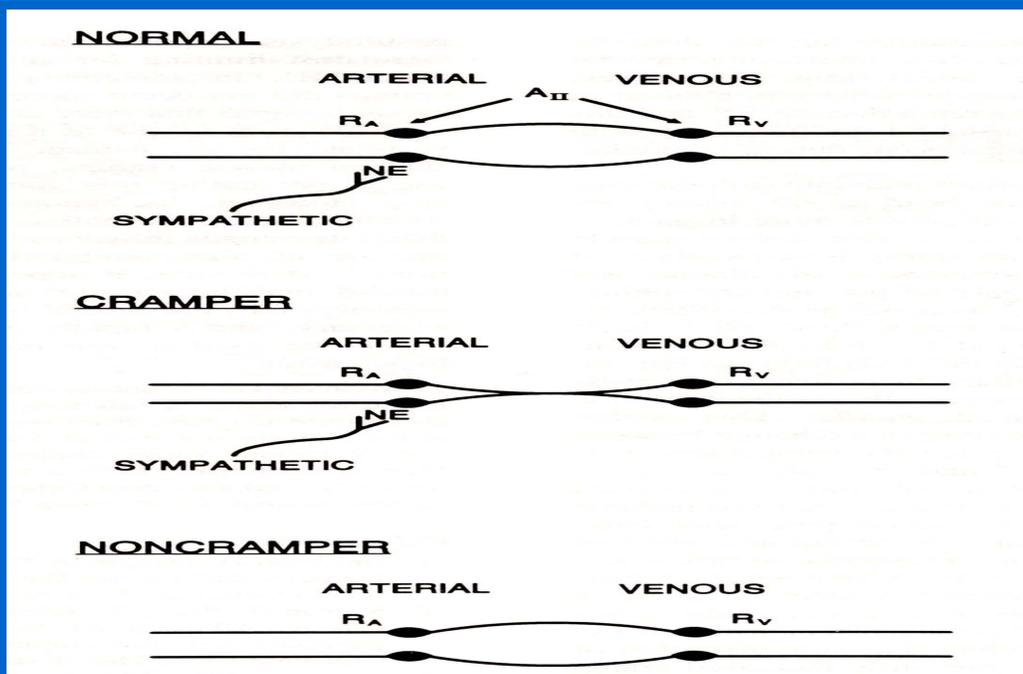


* Kaplan B et al.: Int J Clin Pharmacol Ther Toxicol 1992;30:173-80.

ACTIONS OF ANGIOTENSIN II & SYMPATHETIC NERVOUS SYSTEM



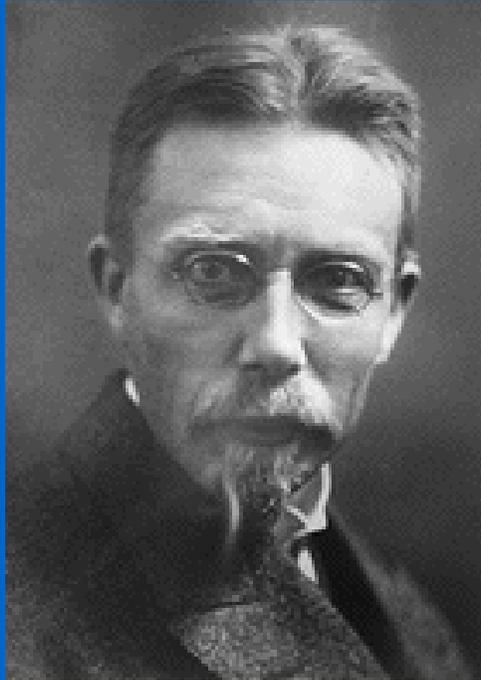
ONLY SOME PATIENTS HAVE DIALYSIS-ASSOCIATED SKELETAL MUSCLE CRAMPS*



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

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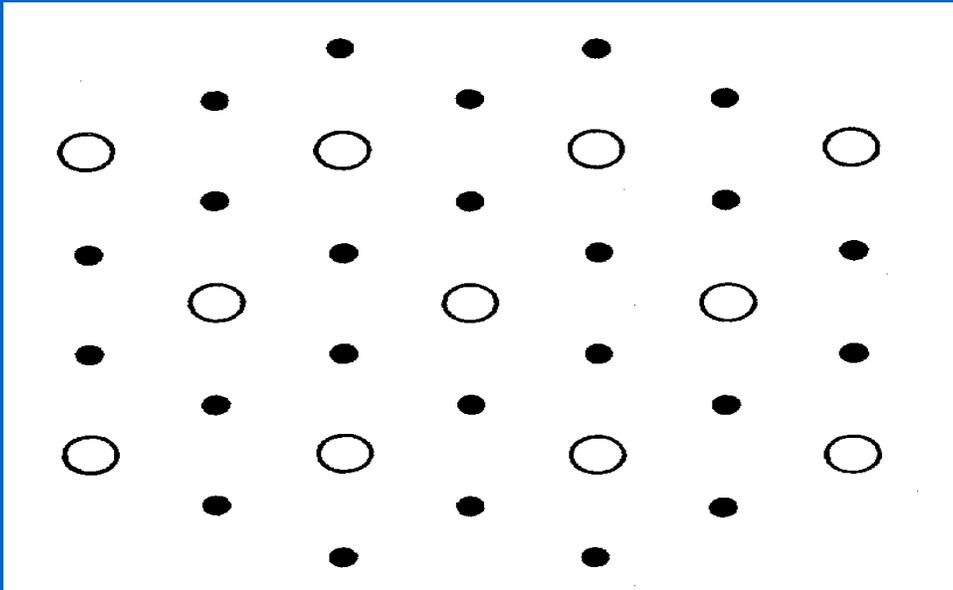
**AUGUST KROGH
1920 NOBEL LAUREATE**



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

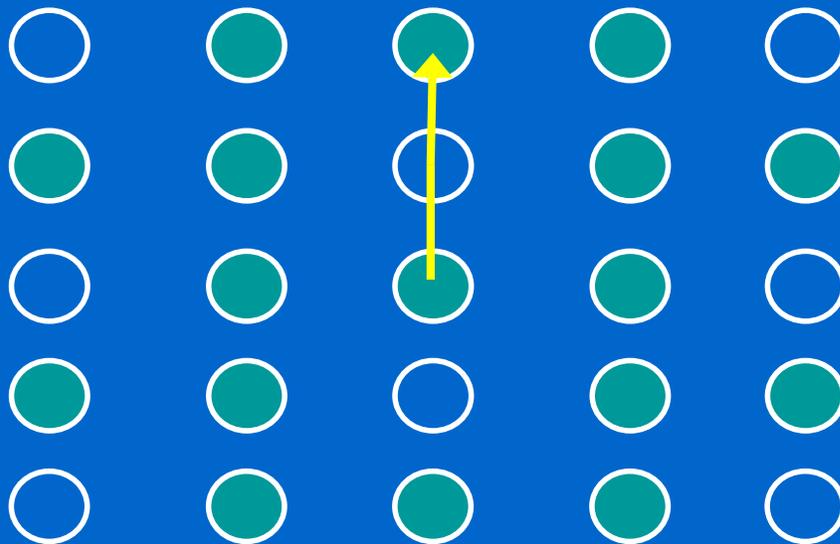


*From Krogh A. Nobel Lecture, December 11, 1920.

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



8 OPEN CAPILLARIES IN MUSCLE CROSS SECTION

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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

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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 ($\downarrow CL_S$)
- IMPACT OF \downarrow SPLANCHNIC BLOOD FLOW ($\downarrow CL_F$) ON BIOAVAILABILITY

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