

PHARMACOKINETICS IN PATIENTS REQUIRING RENAL REPLACEMENT Rx

PART 1: PK IN PATIENTS REQUIRING HEMODIALYSIS

October 22, 2009



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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.

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

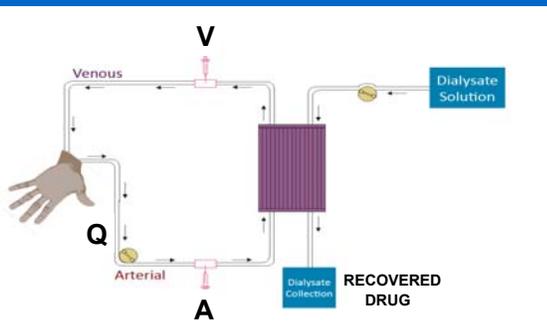


ELIMINATION BY DIFFERENT ROUTES

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

*not actually measured in routine PK studies

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.

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

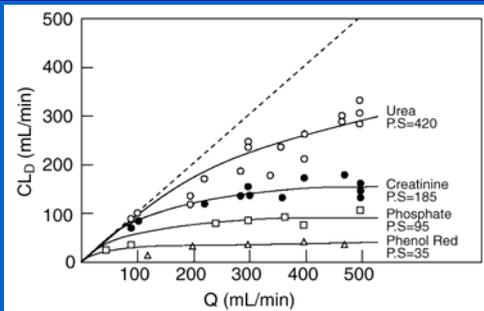
PROCAINAMIDE/NAPA:

RATIO OF DIALYZER PERMEABILITY COEFFICIENTS* 1.28 ± 0.23

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

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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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

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

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:

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

GOALS OF DIALYSIS DISCUSSION

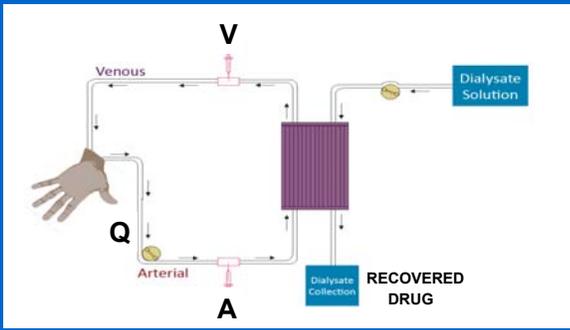
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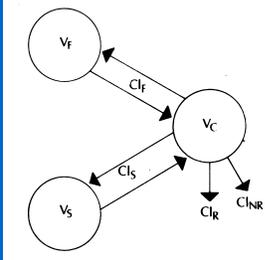
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PATHOPHYSIOLOGIC CONSEQUENCES

DATA SOURCES FOR FICK EQUATION



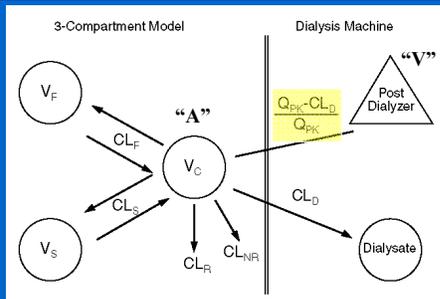
KINETIC MODEL USED TO ANALYZE HEMODIALYSIS DATA*

3-Compartment Model



* 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

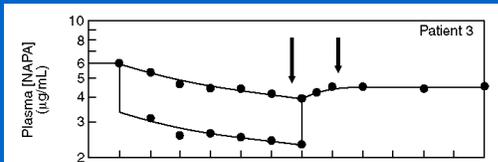
$$CL = Q \left[\frac{A - V}{A} \right]$$

$$CLA = QA - QV$$

$$QV = QA - CLA$$

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

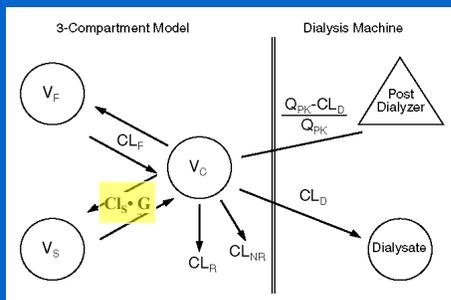
TWO PROBLEMS WITH FIXED-PARAMETER MODEL*



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

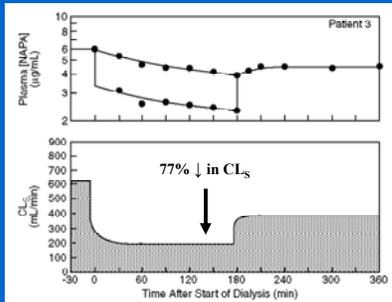
* From Stec GP, et al. Clin Pharmacol Ther 1979;26:618-28.

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.

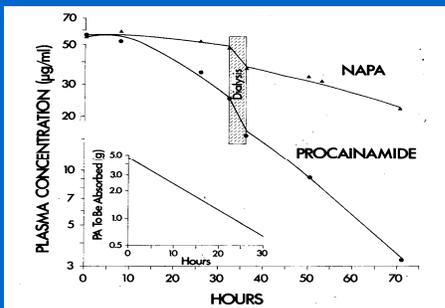
CASE HISTORY (cont.)

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 $\mu\text{g/mL}$ and 33 $\mu\text{g/mL}$, 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 |
| CL_E (mL/min) | 590 | 233 | 66.8 | 16.1 |
| CL_D (mL/min) | | | 68.3 | 45.8 |
| V_{dB} (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?

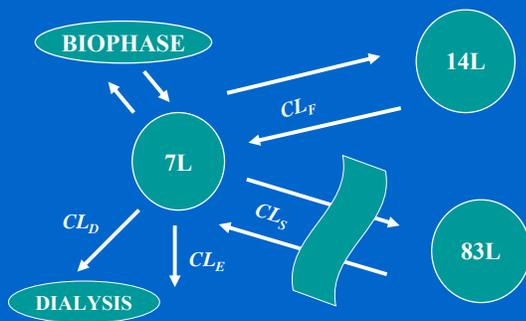
USUAL V_d ESTIMATE :

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

DIALYSIS V_d ESTIMATE :

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

SEQUESTRATION OF DRUG IN SOMATIC TISSUES



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 ↓ DURING DIALYSIS ?

POSSIBILITIES:

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

RENKIN EQUATION*

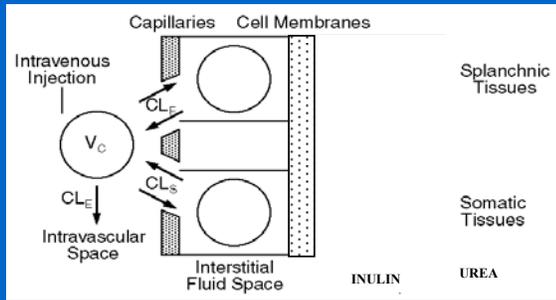
$$CL = Q(1 - e^{-P/Q})$$

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.

MULTICOMPARTMENTAL MODEL OF INULIN AND UREA KINETICS*

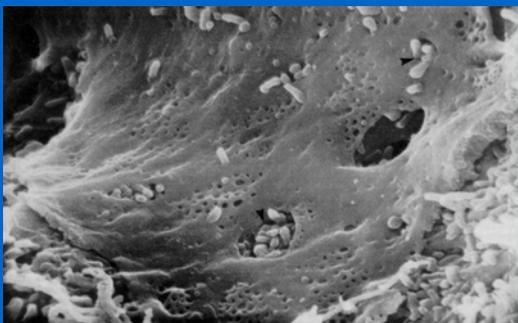


* From Atkinson AJ Jr, et al. Trends Pharmacol Sci 1991;12:96-101.

BASIS FOR KINETIC HETEROGENEITY OF INTERSTITIAL FLUID SPACE

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

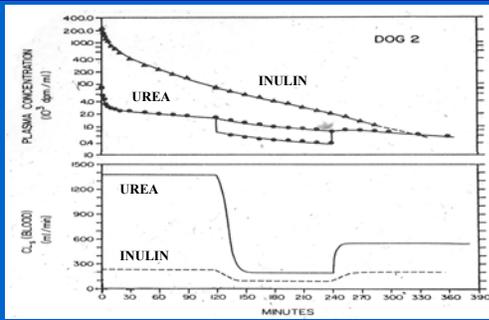
ENDOTHELIAL FENESTRAE IN HEPATIC SINUSOIDS



INTERENDOTHELIAL CELL JUNCTION IN CONTINUOUS CAPILLARY

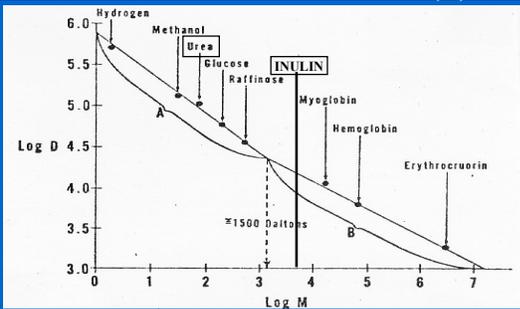


UREA (◐) AND INULIN (◑) KINETICS DURING AND AFTER HEMODIALYSIS*



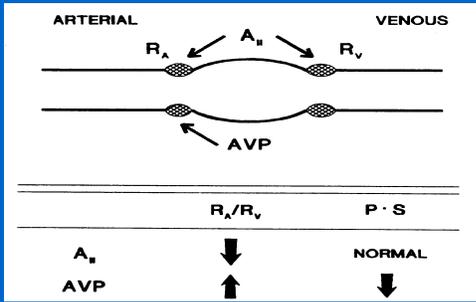
* From Bowsher DJ, et al. J Lab Clin Med 1985;105:489-97.

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



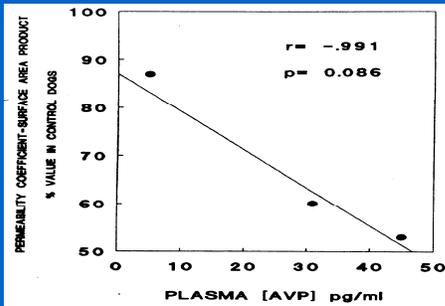
* From Henderson LW: In: Brenner BM, Rector FC Jr. The Kidney. 1976, p. 1643-71.

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 · S*



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

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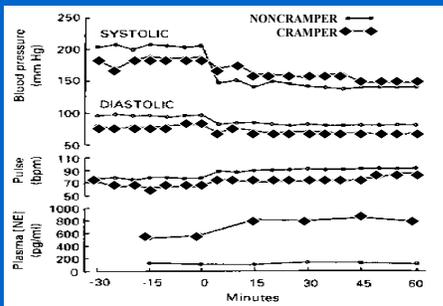
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HEMODIALYSIS-ASSOCIATED SKELETAL MUSCLE CRAMPS

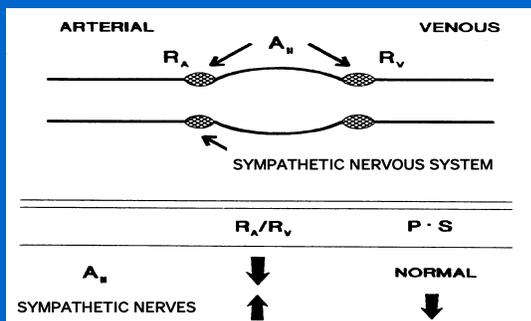
- COMPLICATE MORE THAN 20% OF HEMODIALYSIS SESSIONS
- OCCUR MORE FREQUENTLY IN SOME PATIENTS THAN OTHERS
- PATHOGENESIS UNCLEAR
- SYMPTOMATIC THERAPY: NaCl, MANNITOL
- PREVENTIVE THERAPY: NaCl INFUSION

RESPONSE OF CRAMPING AND NONCRAMPING PATIENTS TO TILT*

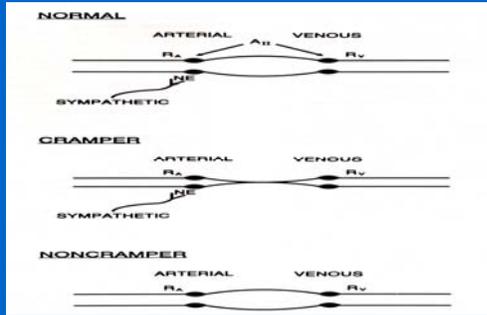


* Kaplan B et al.: Int J Clin Pharmacol Ther Toxicol 1992;30:173-80.

ACTIONS OF ANGIOTENSIN II & SYMPATHETIC NERVOUS SYSTEM

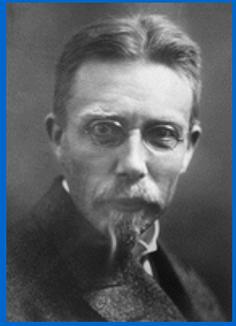


ONLY SOME PATIENTS HAVE DIALYSIS-ASSOCIATED SKELETAL MUSCLE CRAMPS*

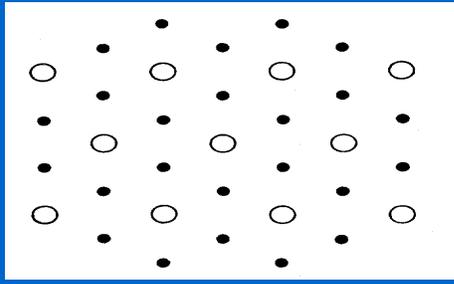


* Sidhom OA, et al. Clin Pharmacol Ther 1994;56:445-51

**AUGUST KROGH
1920 NOBEL LAUREATE**

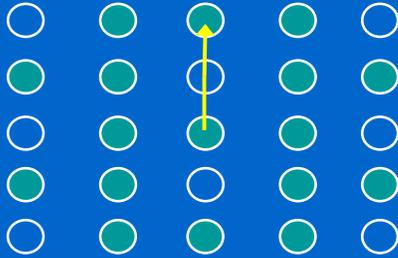


CROSS SECTION OF MUSCLE SHOWING OPEN (O) & CLOSED (●) CAPILLARIES*



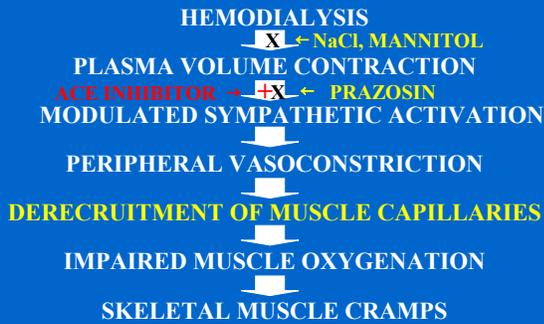
*From Krogh A. Nobel Lecture, December 11, 1920.

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



8 OPEN CAPILLARIES IN MUSCLE CROSS SECTION

**PATHOGENESIS OF DIALYSIS-ASSOCIATED
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 ($\downarrow CL_S$)
- IMPACT OF \downarrow SPLANCHNIC BLOOD FLOW ($\downarrow CL_F$) ON BIOAVAILABILITY
