Anatomy and Physiology of Peritoneal Dialysis

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Outline

- Peritoneal cavity as a dialysis system
- Models of peritoneal transport
- Physiology of peritoneal transport
  - Inverse relationship between solute transport and ultrafiltration
- Kinetics of peritoneal transport
- Synthesis & Application
- Middle Molecules

Anatomy of The Peritoneum

- The lining of the abdominal cavity
- Two layers:

  parietal - lines the anterior wall and undersurface of the diaphragm
  - 20% of total SA; blood supply from abdominal wall

  visceral - covers the abdominal organs
  - 80% of total SA; blood supply from mesenteric aa and portal vv

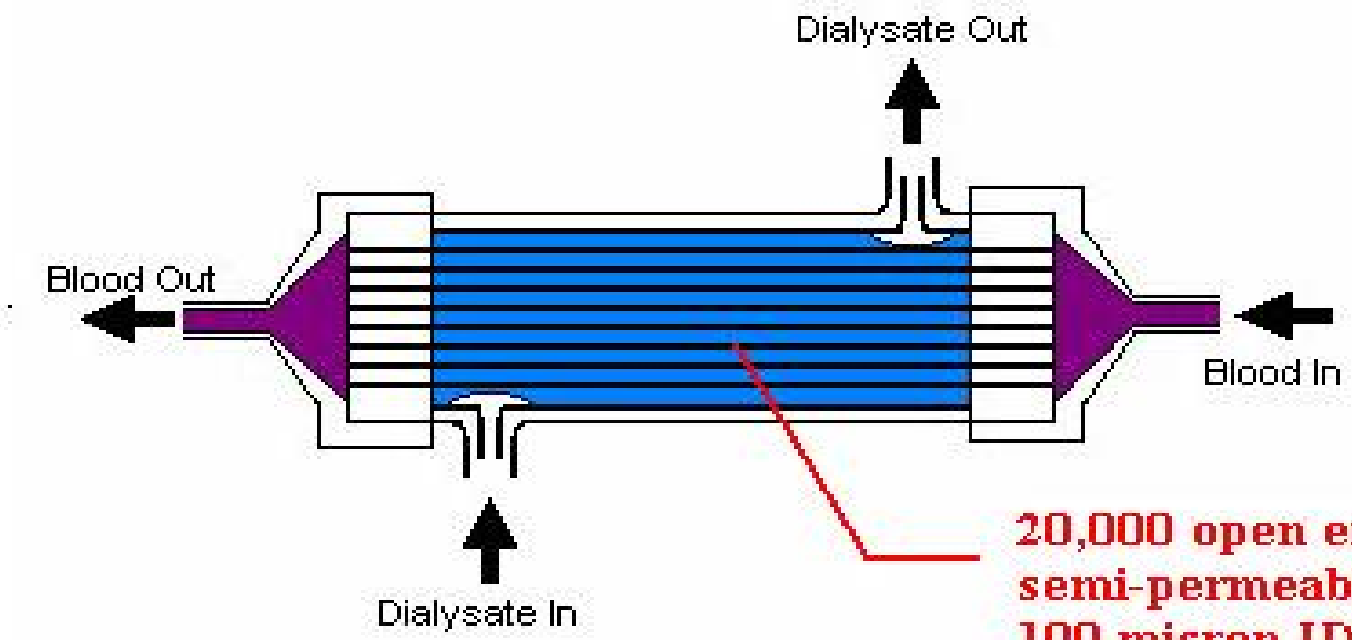
Gokal R, Textbook of PD, pp. 61-70

Anatomy of The Peritoneum

- Size 1.5 – 2 m^2; approximates BSA
- Highly Vascular
- Semi-permeable/bi-directional
- "Lymphatic" drainage through diaphragmatic stomata
- Continuous with Fallopian Tubes in females

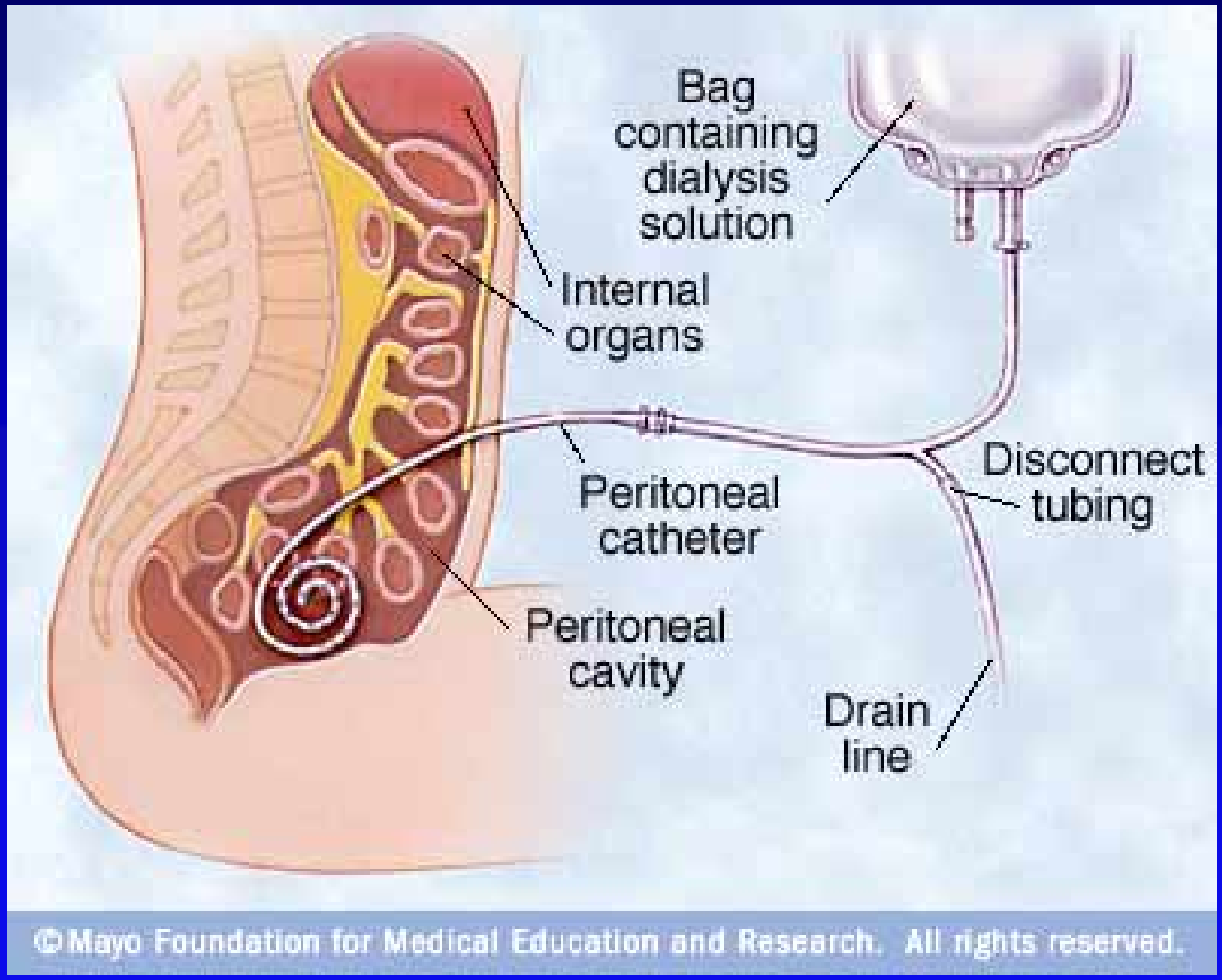
Gokal R, Textbook of PD, pp. 61-70

SCHEMATIC OF A HEMO-DIALYSIS DEVICE



source http://www.shodor.org/master/biomed/physio/dialysis/hemodialysis/fig2.jpg

The Peritoneal Cavity as a Dialysis System



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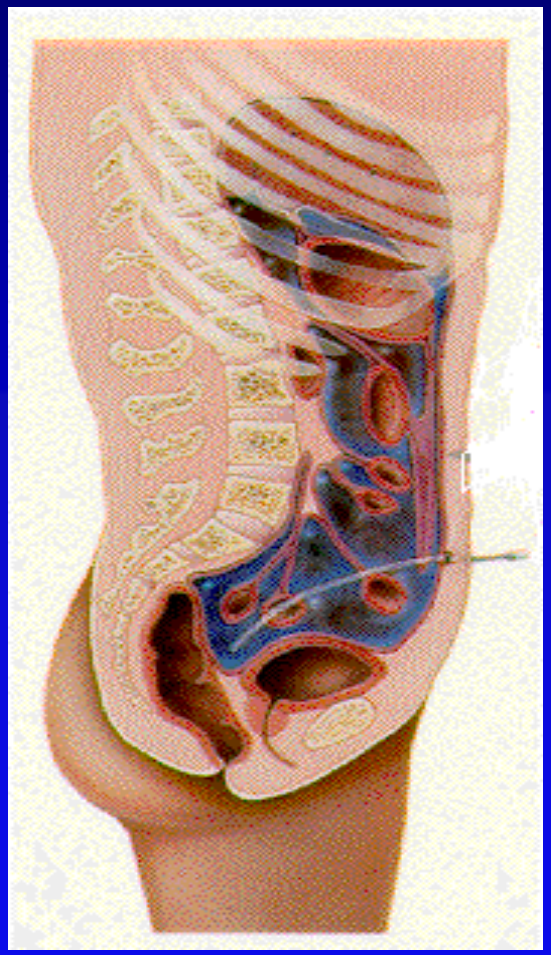
Transport Processes in Peritoneal Dialysis

Diffusion-

Movement of solute from an area of higher concentration to an area of lower concentration



Osmosis-

Movement of water from an area of higher concentration (lower solute concentration) to an area of lower concentration (higher solute concentration)

Models of Peritoneal Transport

- The three pore model
- The pore- matrix model
- The distributed model

Transport Across the Peritoneal Endothelium: *The Three Pore Model*

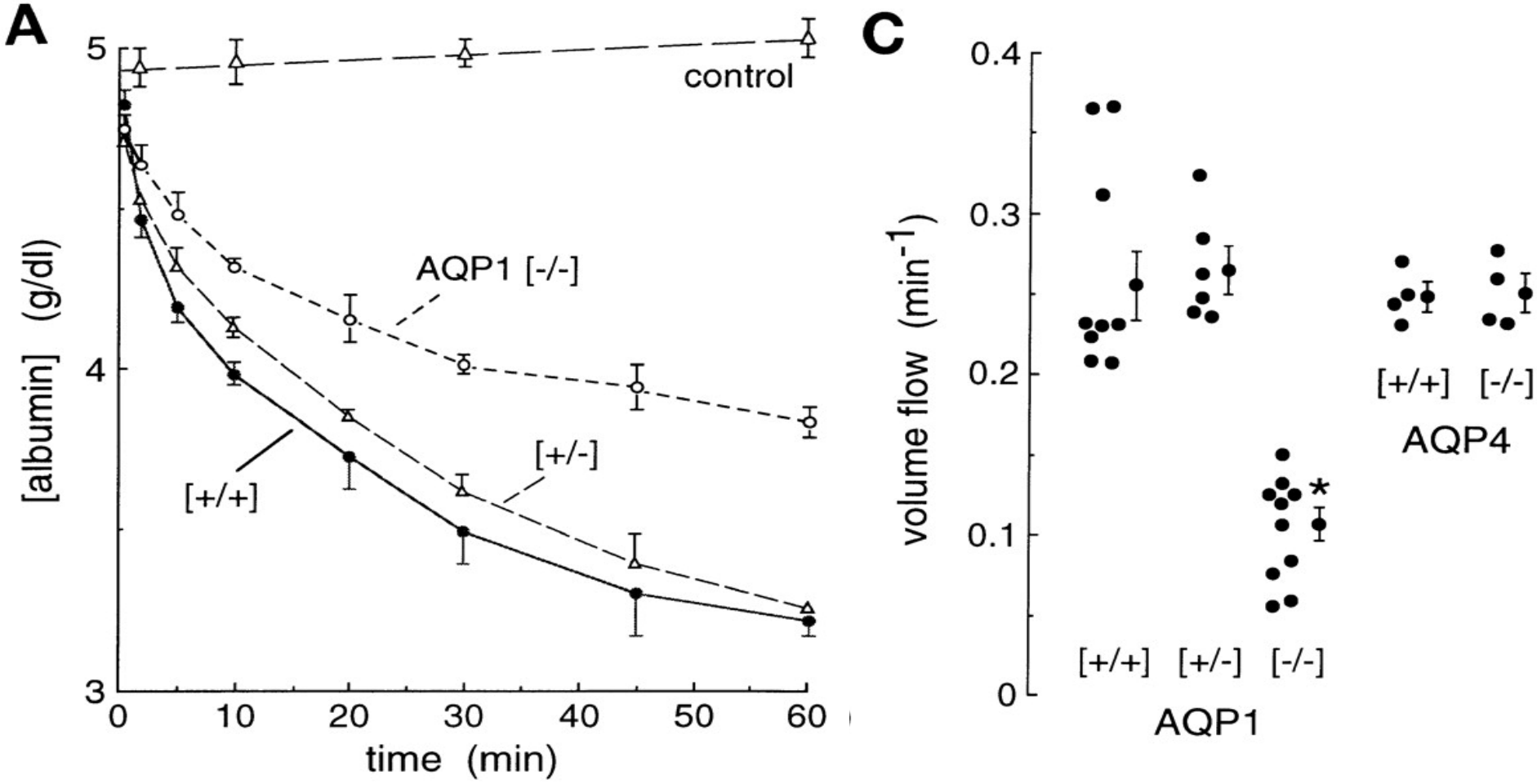
- **Large pores (100 - 200 Å)**
  - few in number (3% of SA)
  - transport macromolecules
  - clefts between endothelial cells

- **Small pores (40 - 60 Å)**
  - most numerous (95% of SA)
  - allow transport of small solutes and water
  - postulated to be clefts in the endothelium; have not been demonstrated anatomically

Transport Across the Peritoneal Endothelium: *The Three Pore Model* (cont'd)

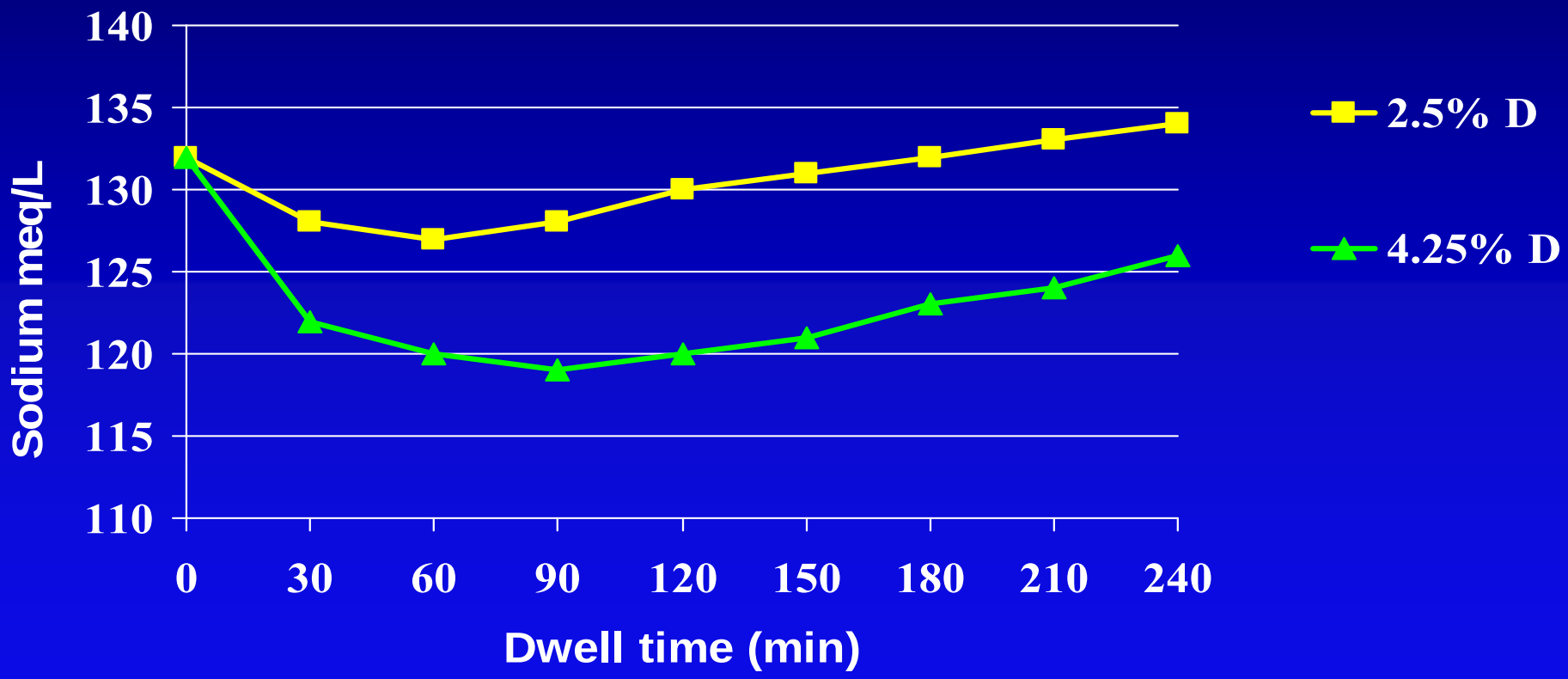
- **Ultrasmall (transcellular) pores (4 - 6 Å)**
  - many in number (but only 2% of SA)
  - transport water only (Na sieving)
  - **Demonstrated** to be AQP 1

Water Transport in Aquaporin- 1 Knockout Mice



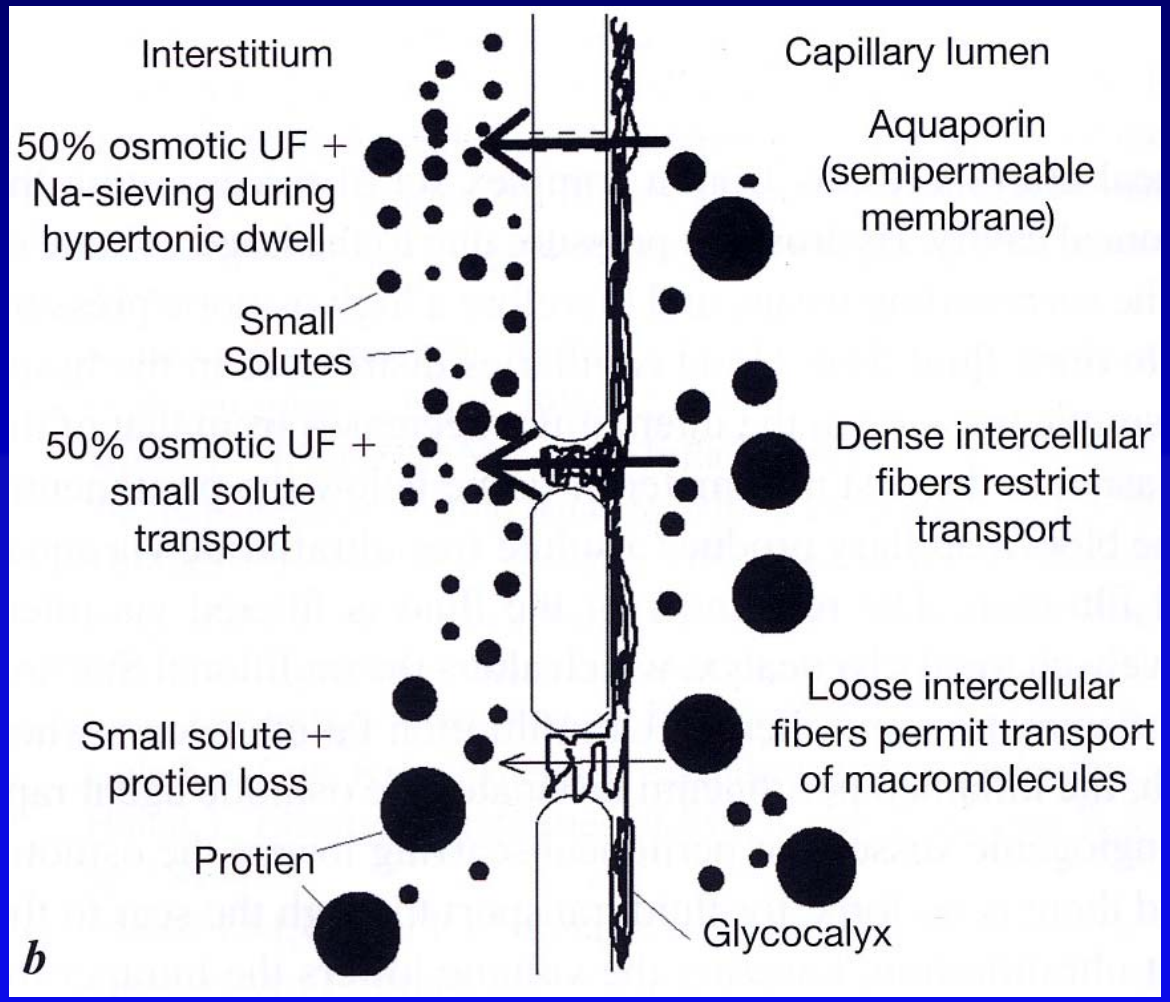
Yang et al. AJP 276:C76, 1999

Changes In Dialysate Sodium During Dwell (Sodium Sieving)



Heimburger et al. Kid Int 38: 495, 1990

Ultrafiltration in PD: The Pore-Matrix Model



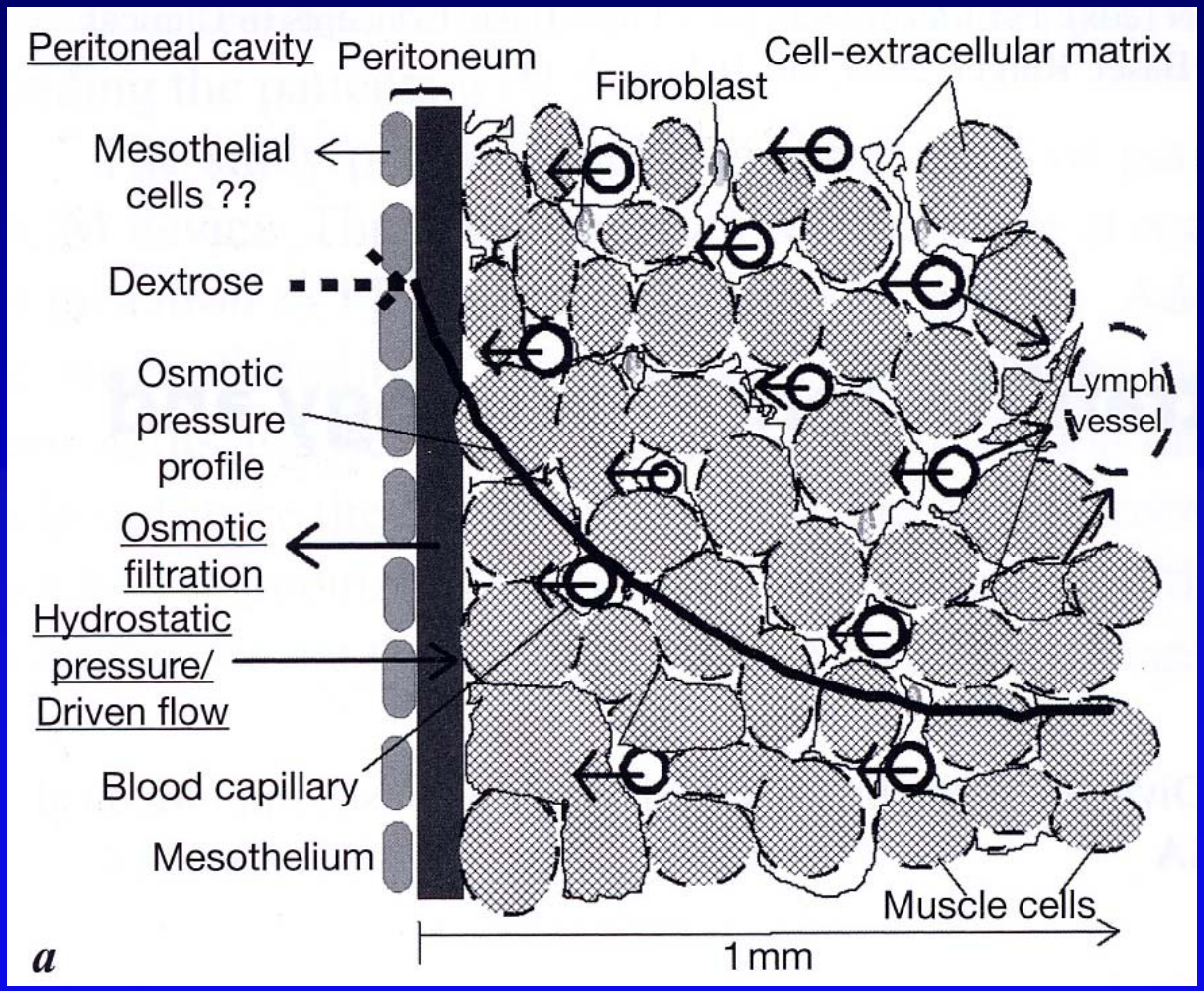
Flessner M. Contrib Nephrol 163:7, 2009

Ultrafiltration in PD: The Pore-Matrix Model

- The small and large pores represent different functional states of a single entity that depends on the density of the glycocalyx.

- The glycocalyx density is decreased by:
  - Oxidized LDL
  - Adenosine
  - Ischemia reperfusion injury
  - TNF α

Ultrafiltration in PD: The Distributed Model



Flessner M. Contrib Nephrol 163:7, 2009

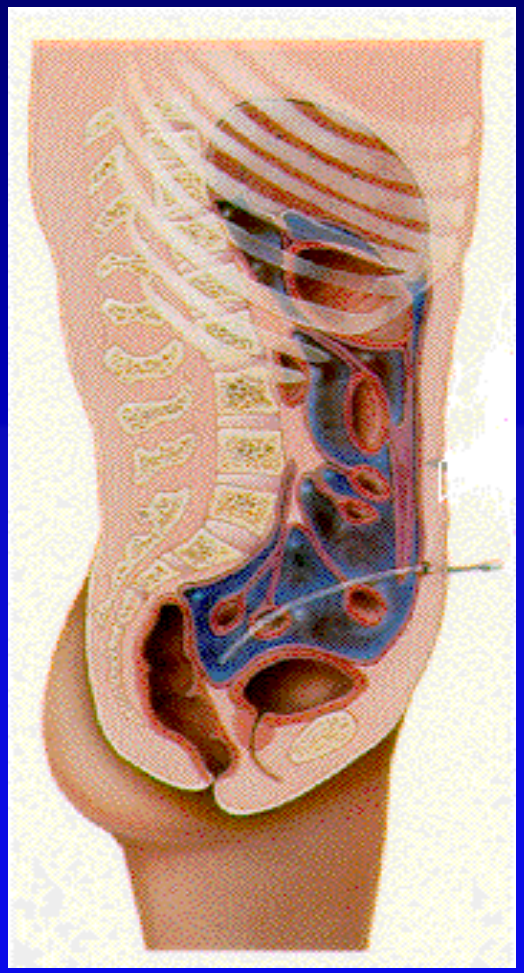
Effective Peritoneal Surface Area

- Increased “effective” peritoneal surface area may occur:
  - During peritonitis
  - After prolonged exposure to high glucose-containing fluids

Two Clinical Endpoints for Peritoneal Transport

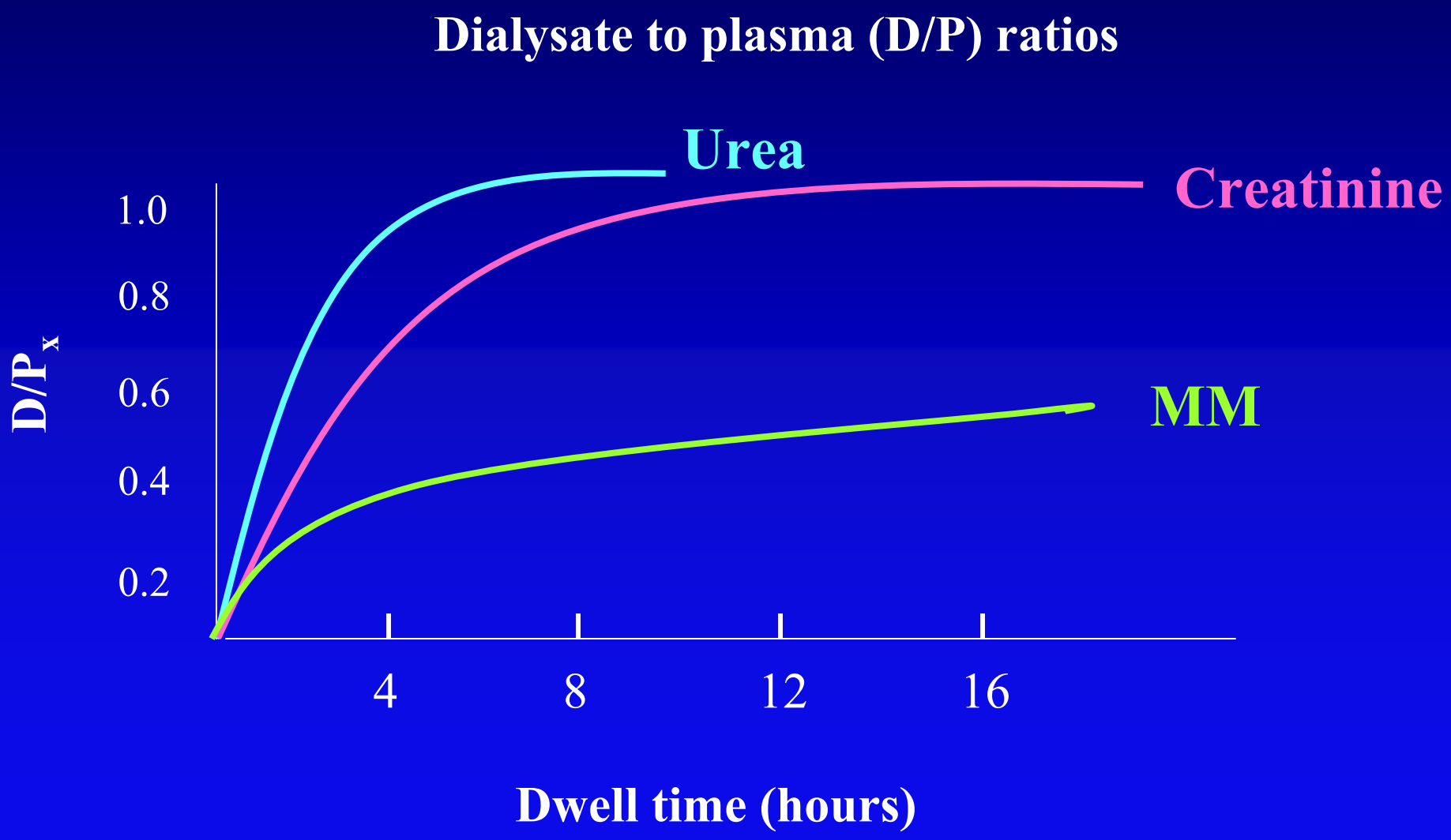
- **Solute Clearance**
  - diffusive
  - convective
- **Fluid Removal**

Factors Influencing Solute Diffusion



- Surface Area
- Peritoneal Permeability
- Solute Characteristics
- Concentration Gradient
- Temperature of Dialysis Solution
- Blood Flow
- Dialysis Solution Volume in 24 hrs.
- Dwell Time

Diffusion Curves for Solutes of Varying Size



Diffusion Kinetics – *From Blood to Dialysate*

- Diffusive flux is highest in the first hour- the gradient is largest- and decreases over time
- By 4 hours, urea is > 90% equilibrated, creatinine > 60% equilibrated
- Further small solute removal is modest
- Long dwells more important for removal of ***middle*** MW solutes (e.g. β_2MG)

Factors Influencing Ultrafiltration

- Surface area
- Peritoneal membrane permeability
- Pressure gradients
  - hydrostatic
  - oncotic
  - osmotic (really hydrostatic; 1 mOsm = 17 mm Hg)

What Determines Transcapillary Ultrafiltration?

$$J_v = L_p S \left[P_{plasma} - P_{if} - \sum_{i,j} \alpha_j \sigma_{i,j} \left(\pi_{i,plasma} - \pi_{i,if}\right)\right]$$

J_v	flow/area
L_p	hydraulic conductivity
S	total pore area
P_{plasma}	intraluminal capillary hydrostatic pressure in plasma
P_{if}	interstitial fluid hydrostatic pressure
α_j	Fraction of the total pore area that is made up of the j^{th} pore
$\sigma_{i,j}$	Reflection coefficient of the j^{th} pore for the i^{th} solute
$\pi_{i,plasma}$	Osmotic pressure in plasma due to the i^{th} solute
$\pi_{i,if}$	Osmotic pressure in the interstitium due to the i^{th} solute

Flessner M. Kid Int 69:1494, 2006

Or, in English…

Average UF rate (ml/min) =

hydraulic conductivity (cm/min/mmHg) x
total effective pore area (cm^2) x
[average osmotic pressure + net trans-membrane hydrostatic pressure - net oncotic pressure (mm Hg)]

Factors Influencing Ultrafiltration

- Ideally we'd like to use a solute with reflection coefficient (RC) ~ 1.0. Glucose has a reflection coefficient of 1.0 for AQP-1 but this accounts for only 2% of SA.

- Despite having RC only ~ 0.05 for the small pore, adding glucose to PD fluid creates an osmotic gradient and moves water from the blood into the peritoneal cavity.

Effect of Glucose Absorption

Therefore, a major determinant of the average UF per exchange is the "average $\sigma_{glucose}$", as this will affect the rate of glucose absorption and the speed of decline of the glucose gradient.

Membrane Permeability and Ultrafiltration – "*slow transporters*"

the "***tighter***" the peritoneal membrane (higher mean σ_{glu})

↓

the ***slower*** will glucose diffuse out of the peritoneal cavity

↓

the osmotic gradient will be maintained ***longer***

↓

the ***more*** ultrafiltration will take place

Membrane Permeability and Ultrafiltration – "*rapid transporters*"

the "***leakier***" the peritoneal membrane (lower mean σ_{glu})

↓

the ***faster*** will glucose diffuse out of the peritoneal cavity

↓

the ***faster*** the osmotic gradient will dissipate

↓

the ***less*** ultrafiltration will take place

The Peritoneal Equilibration Test

How easily does solute (creatinine) cross from the blood to the peritoneal cavity?

- Quantified as $\frac{\text{Dialysate creatinine concentration}}{\text{Plasma creatinine concentration}}$

or

D/P creatinine (at t = 4 hours)

The Peritoneal Equilibration Test

How long is glucose retained in the peritoneal cavity?

- Quantified as:

$$\frac{\text{Dialysate concentration of glucose at t = 4hrs}}{\text{Dialysate concentration of glucose at t = 0 hr}}$$

or

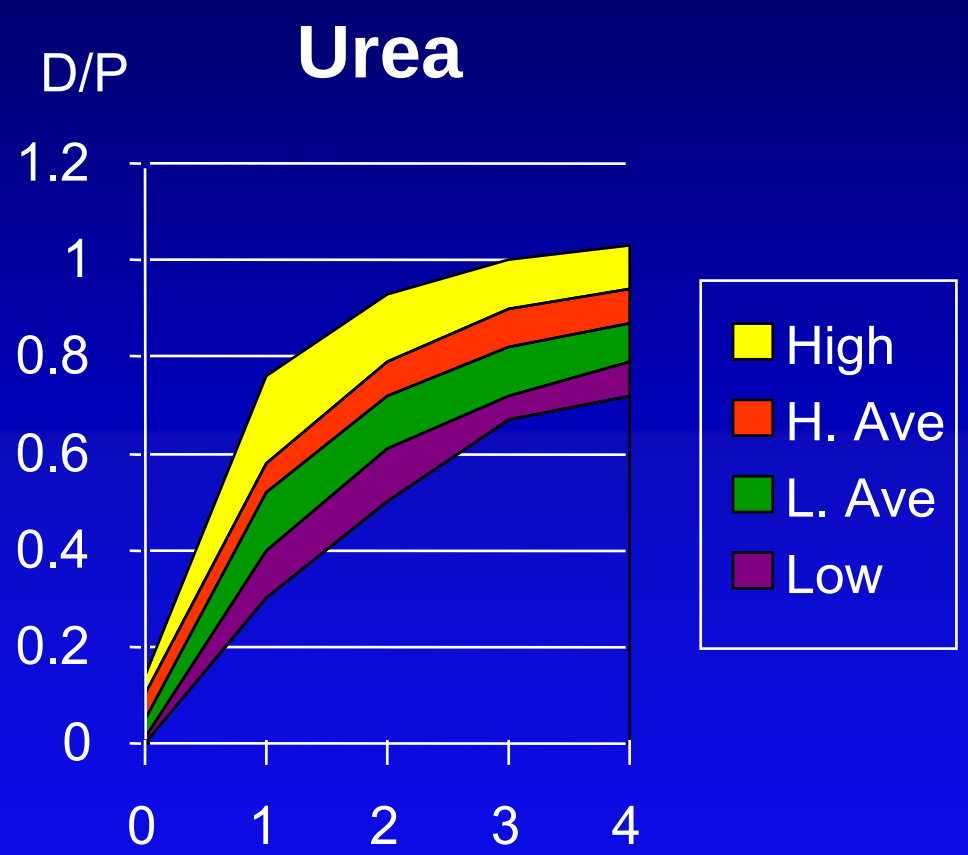
D/D_0 glucose (at t = 4 hours)

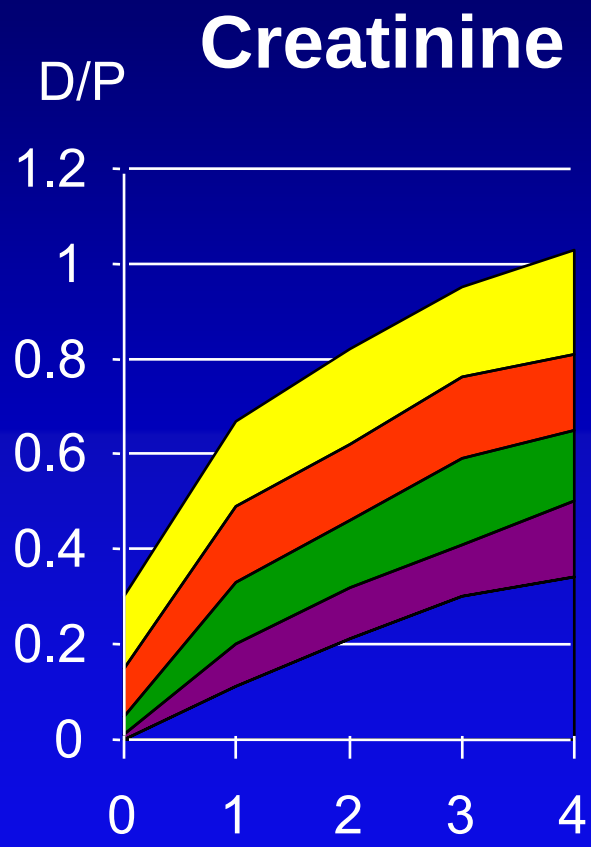
- *cannot use D/P glucose as a surrogate since glucose entering the plasma from dialysate is rapidly metabolized*

Peritoneal Equilibration Test Protocol

- 2L of 2.5% dextrose dialysate is infused with the patient supine after complete drain of a long ($\geq$ 8 hrs) 2 L dwell.
- Blood and dialysate samples are taken immediately after infusion and at 2 and 4 hours for measurements of urea, creatinine, and glucose.
- Patient is drained upright after 4 hours and drain volume is recorded.

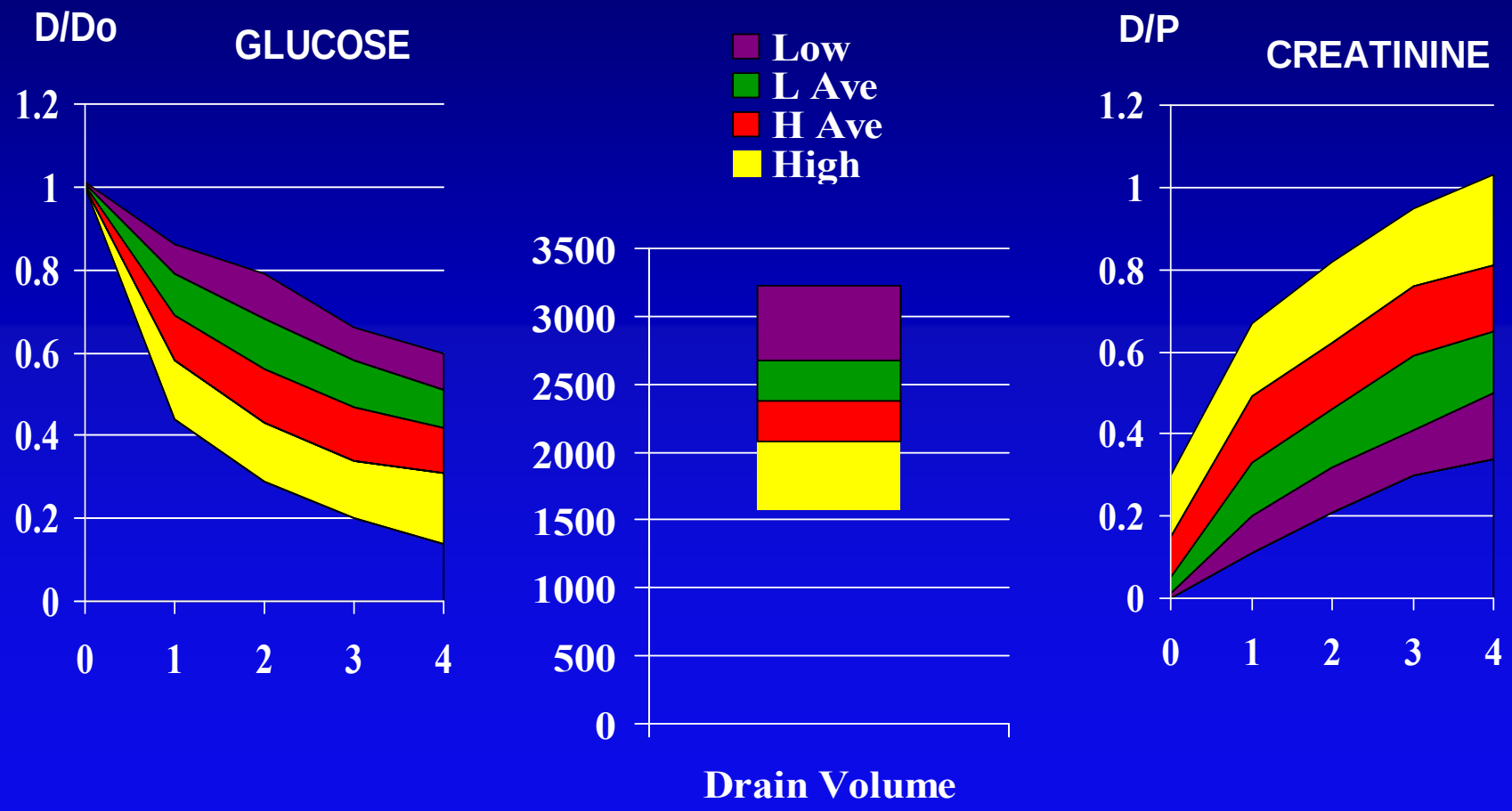
Standard Peritoneal Equilibration Test (2.5% Dextrose)





Twardowski et al. PDB 7; 138, 1987

Standard Peritoneal Equilibration Test (2.5% Dextrose)



Twardowski et al. PDB 7: 138, 1987

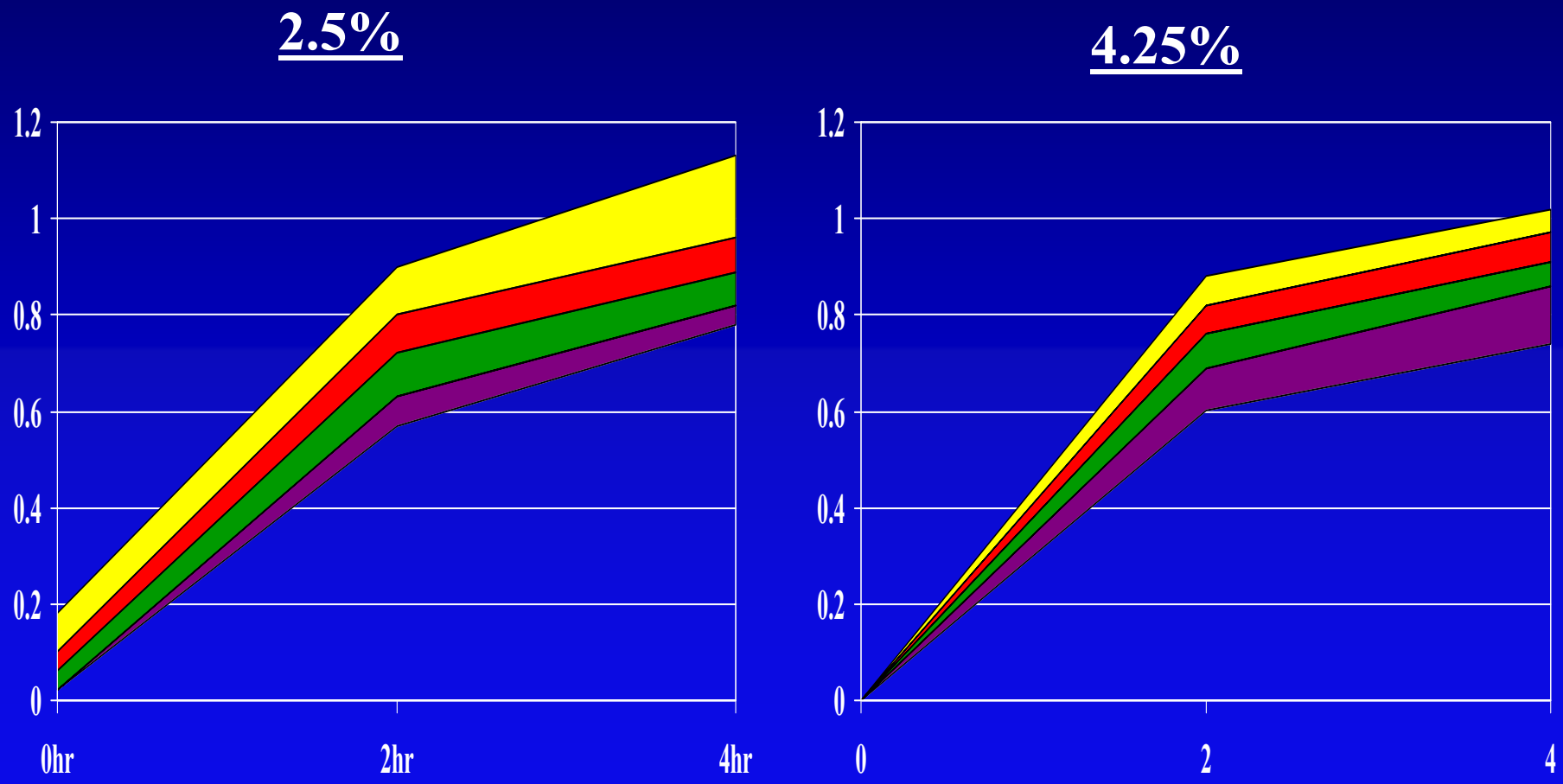
Modified Peritoneal Equilibration Test

- Similar to the standard PET except,
- Performed with 4.25% dextrose, thereby creating a large osmotic gradient.

Modified Peritoneal Equilibration Test

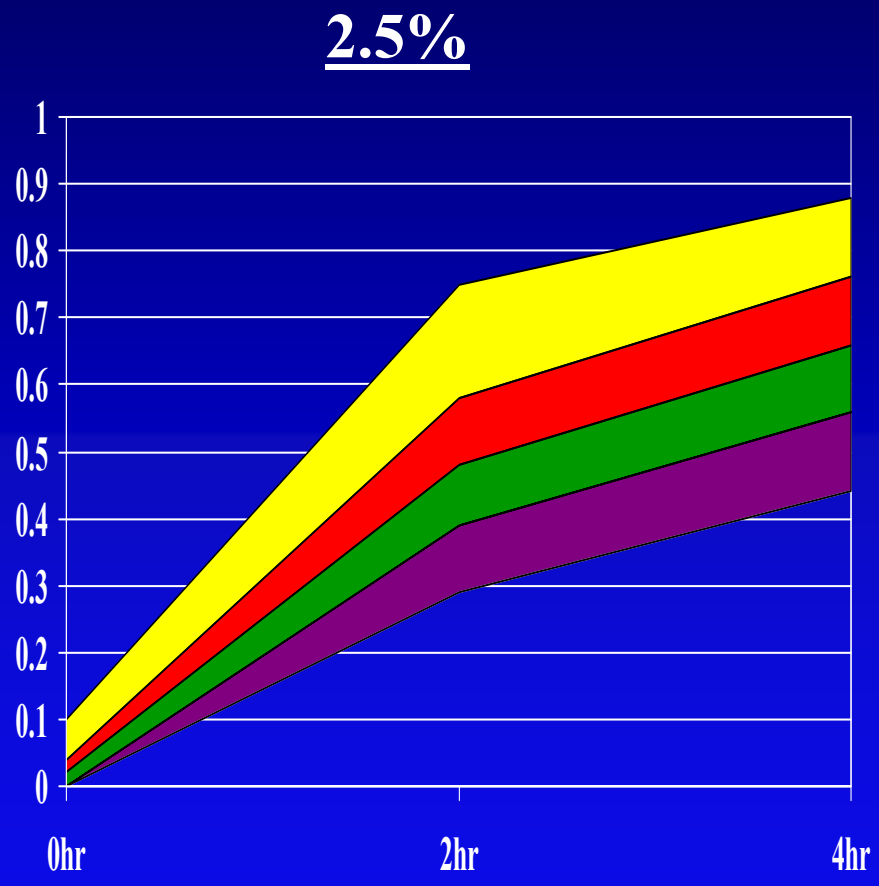
- Ultrafiltration failure is defined as net ultrafiltration < 400 cc at 4 hours
- Correlates well with clinical behavior.

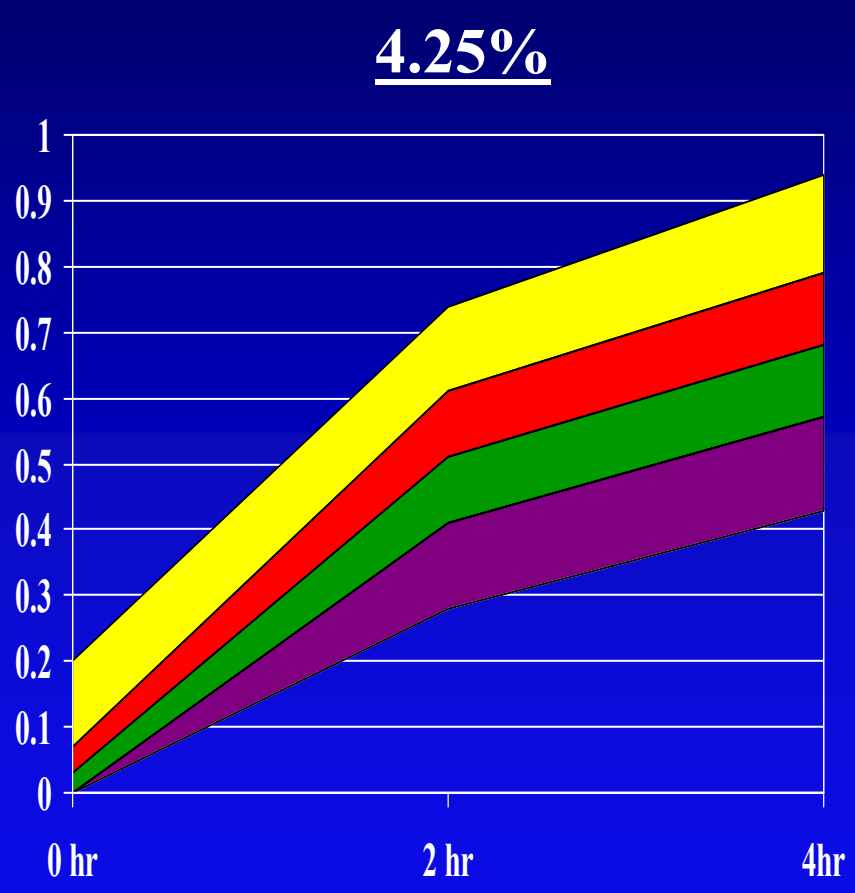
Comparison of D/P Urea Obtained by 2.5% and 4.25% PET



Pride et al. Perit Dial Int 22:365, 2002

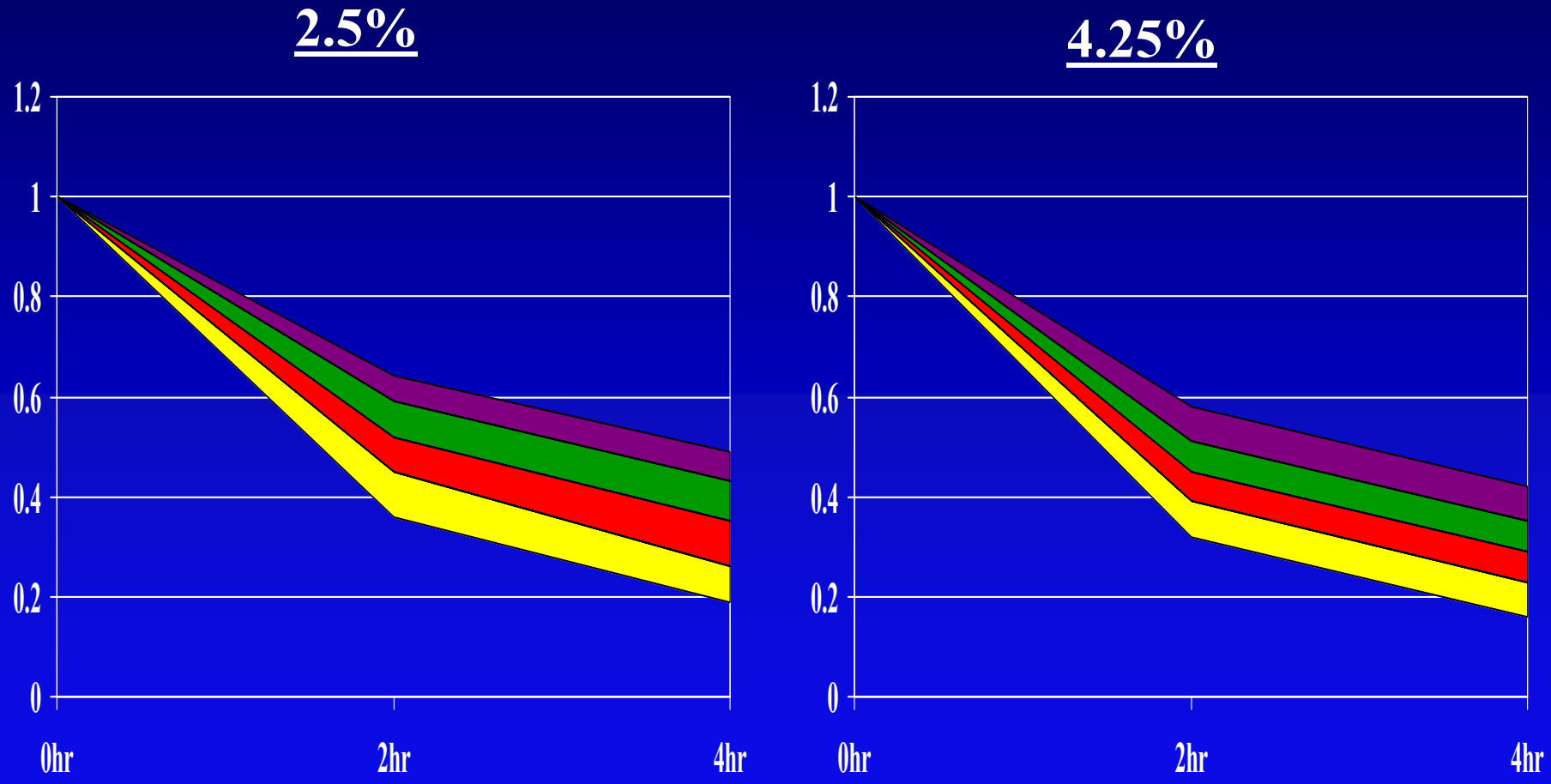
Comparison of D/P Creatinine Obtained by 2.5% and 4.25% PET





Pride et al. Perit Dial Int 22:365, 2002

Comparison of D/D_0 Glucose Obtained by 2.5% and 4.25% PET



Pride et al. Perit Dial Int 22:365, 2002

Discordance (> 1 Category) Between 2.5% and 4.25% PET at 4 Hours

D/P_{urea}	3/47
D/P_{creat}	1/47
$D/D_{0\ glu}$	0/45

Pride et al. Perit Dial Int 22:365, 2002

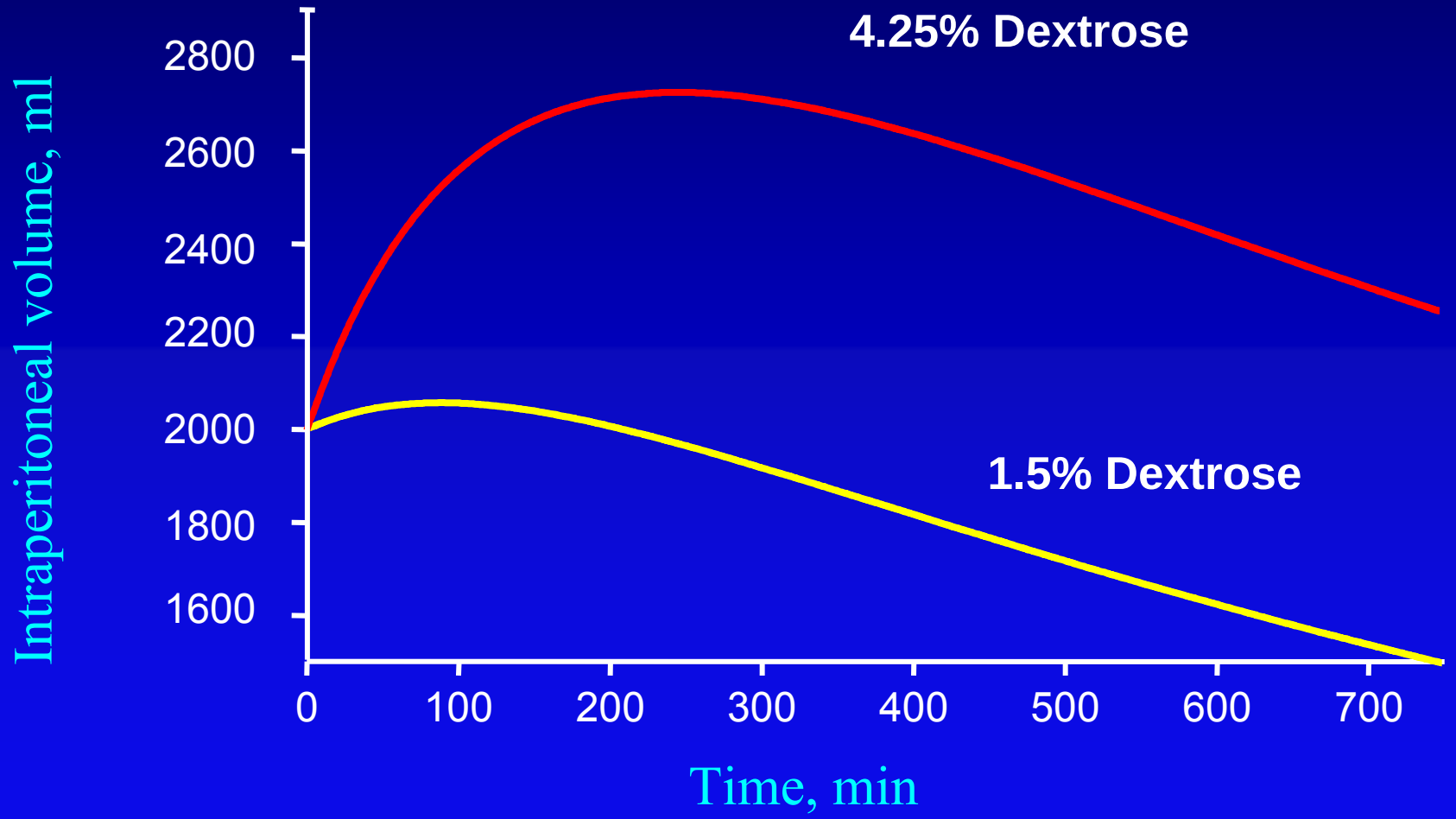
- A PET using 4.25% dextrose may be substituted for the standard 2.5% PET. This allows for simultaneous evaluation of both the small solute transfer and ultrafiltration capacities of the peritoneal membrane.

- However, commercially available programs for modeling peritoneal adequacy have not been standardized to the 4.25% PET.

When Should the PET be Performed?

- A PET performed during the first month of PD is often unreliable. This is especially likely if the initial PET shows the patient to be a low/average transporter.
- Therefore, the initial PET should ideally be done after 4-6 weeks of PD.
- A PET should not be done within a month of an episode of peritonitis.
- The PET need not be routinely repeated; it should be repeated only if clinically warranted.

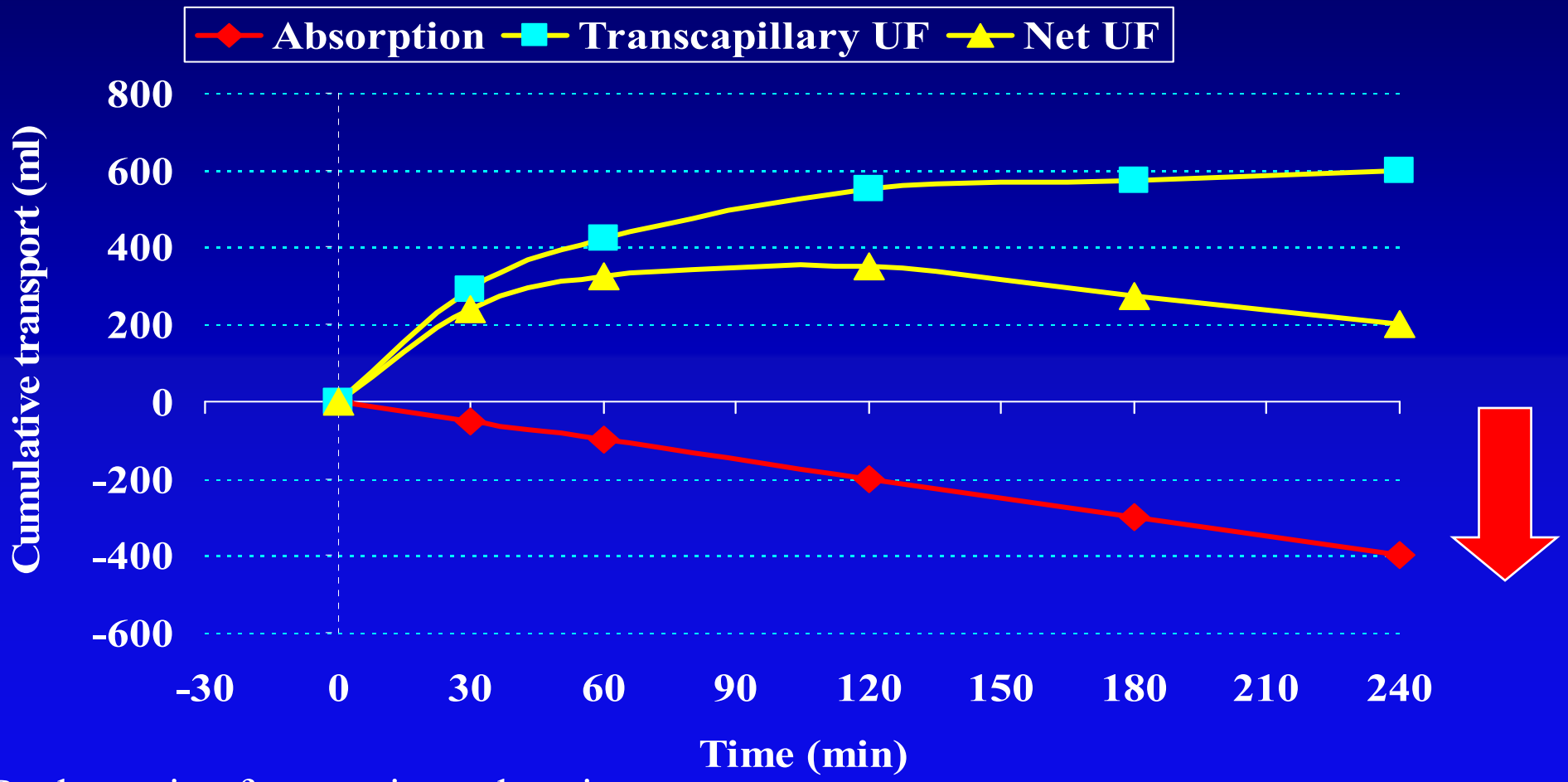
Ultrafiltration with Different Strengths of Dialysate



Fluid Absorption from the Peritoneal Cavity

- Occurs directly via lymphatics (~ 10%)
- Also via absorption across tissues
- Difficult to measure but ~ 1-2 ml/min
- These processes are “bulk flow” and therefore detract from solute and fluid removal

Balance of Opposing Forces



Reabsorption from peritoneal cavity

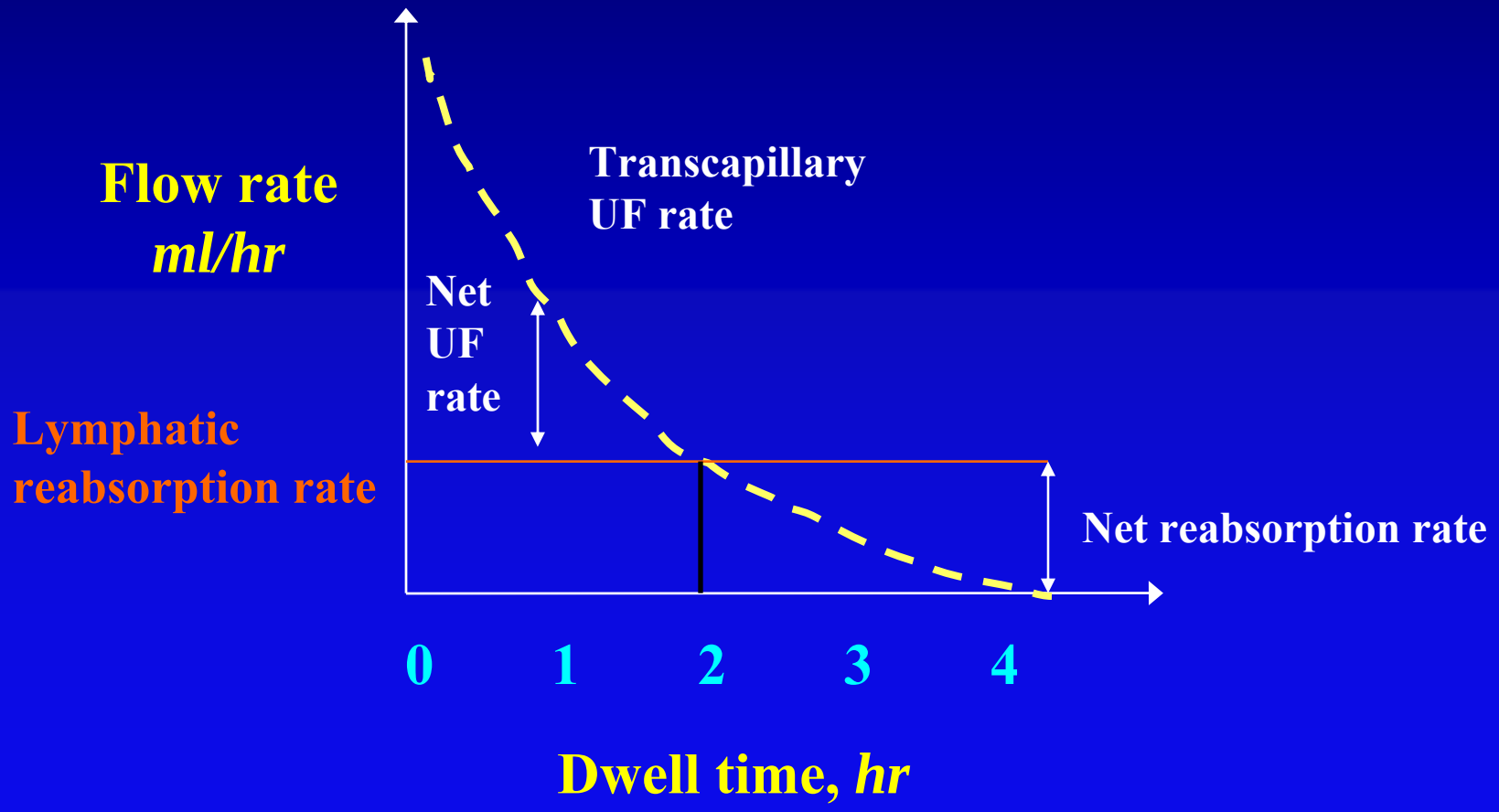
Mactier et al. JCI 80:1311, 1987

What Happens To Intraperitoneal (IP) Volume During a Dwell?

Assume 2L, average D/P, 2.5% Dextrose

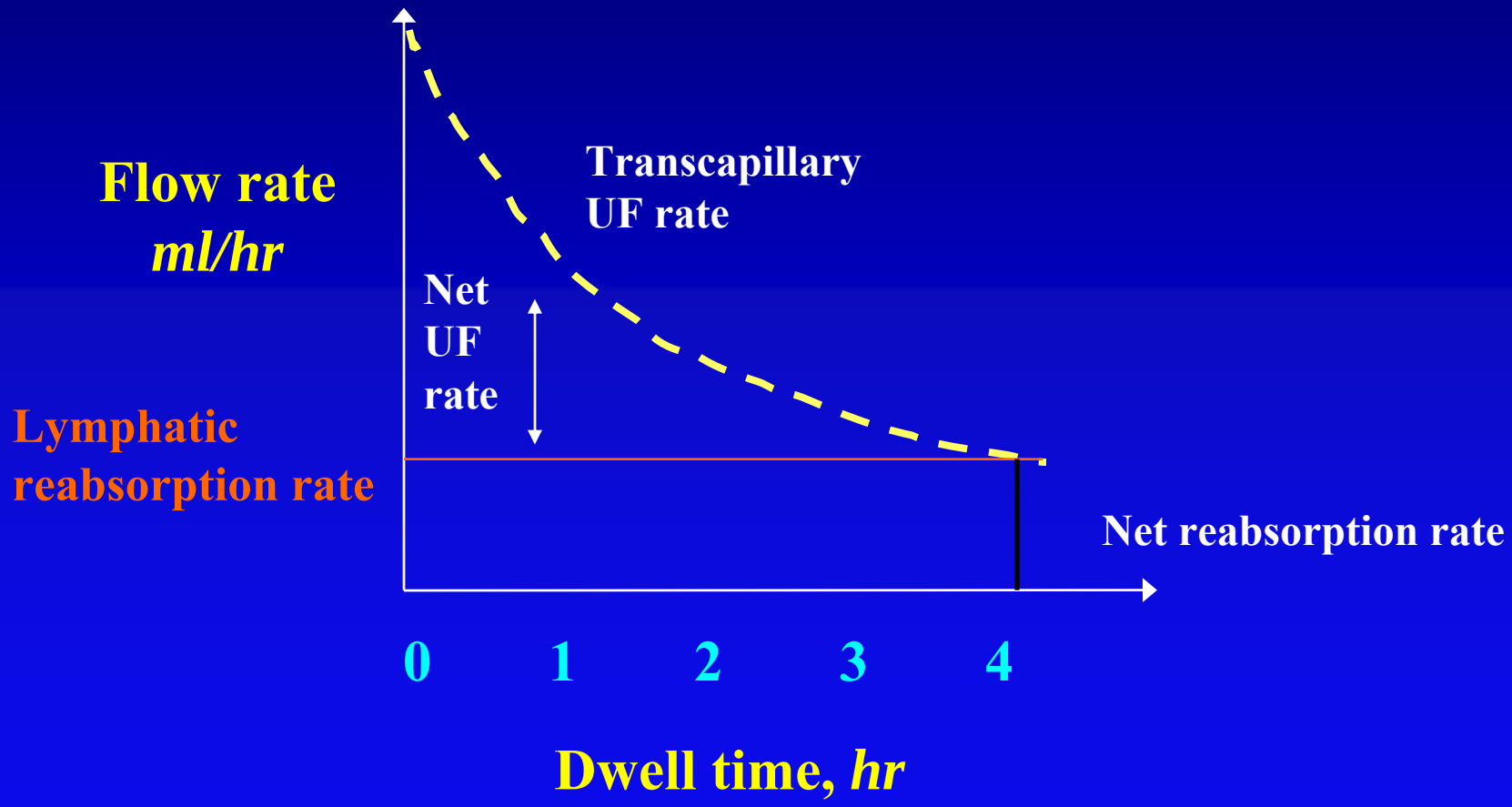
- UF maximal at start (about 15 ml/min)
- UF decreases as glucose is absorbed from the peritoneal cavity and osmotic gradient lessens
- IP volume slowly increases until lymphatic reabsorption (LR) rate = UF rate
- Once LRR > UFR, IP volume begins to decrease
- After osmotic equilibrium is reached UF ceases; IP volume continues to decrease by virtue of LR

Net UF and Lymphatic Reabsorption Rates During 2.5% Dextrose Dialysis Dwell

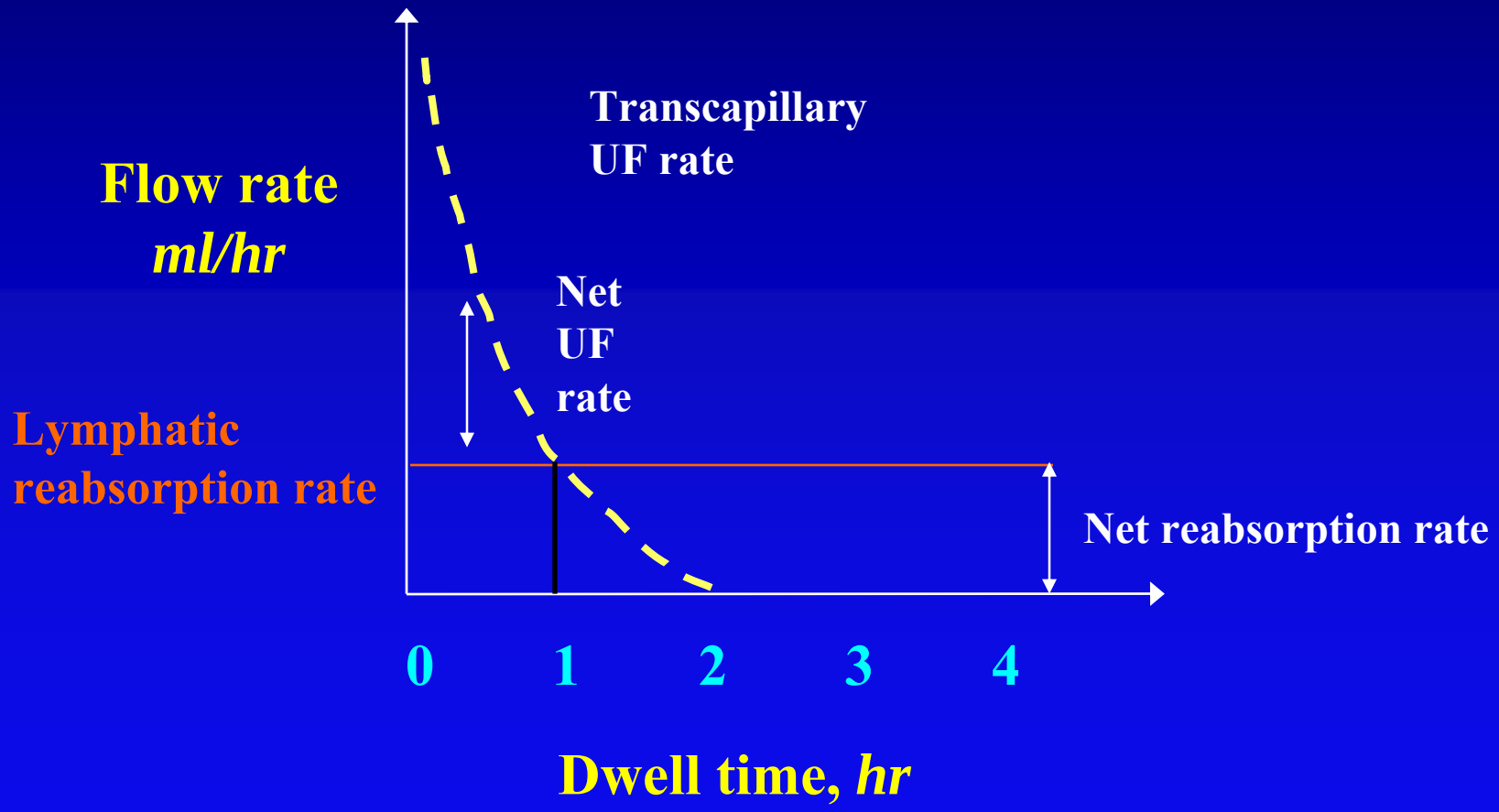


Mactier et al. Kid Int 32:165, 1987

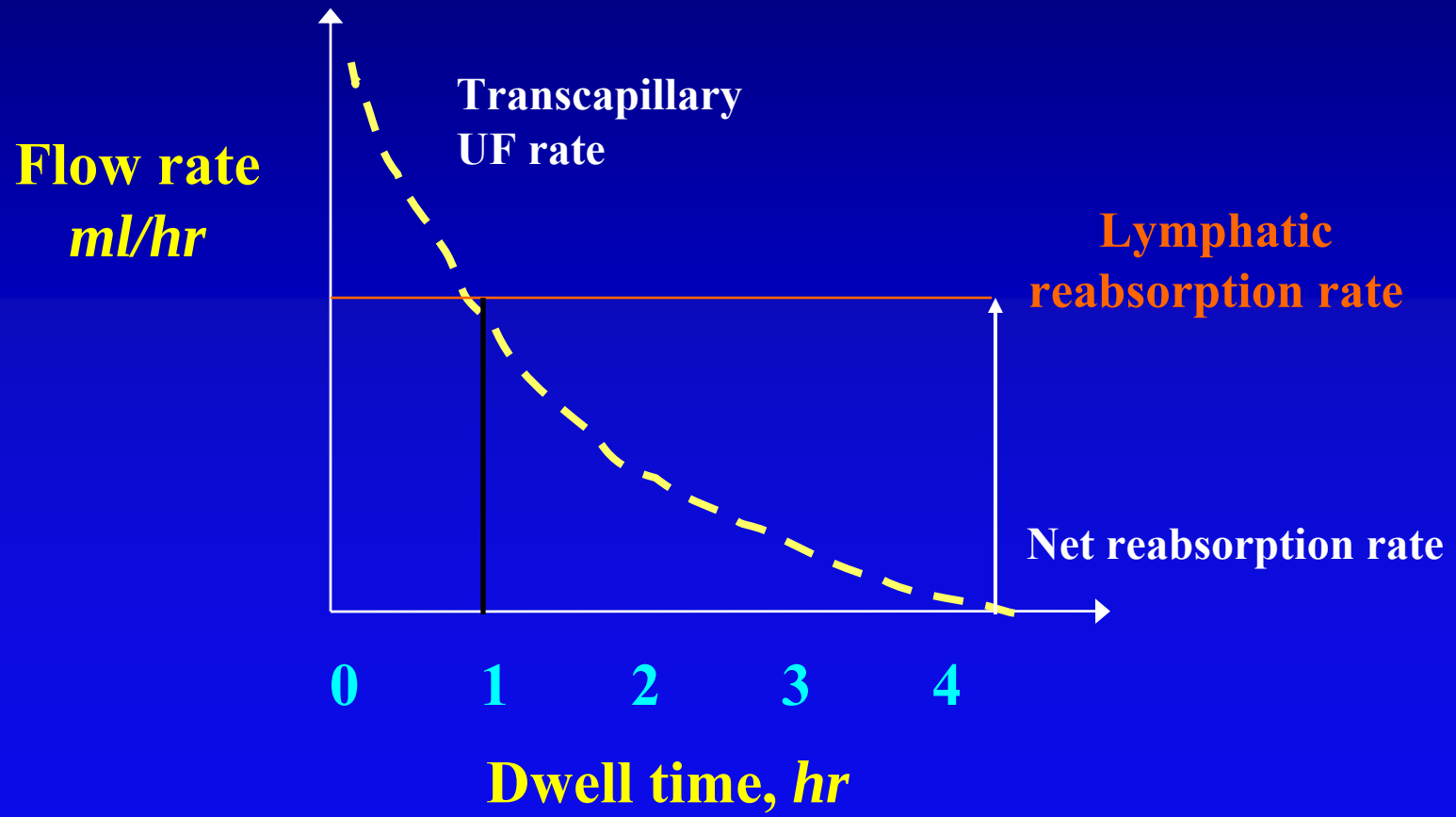
Net UF and Lymphatic Reabsorption Rates in a Low Transporter



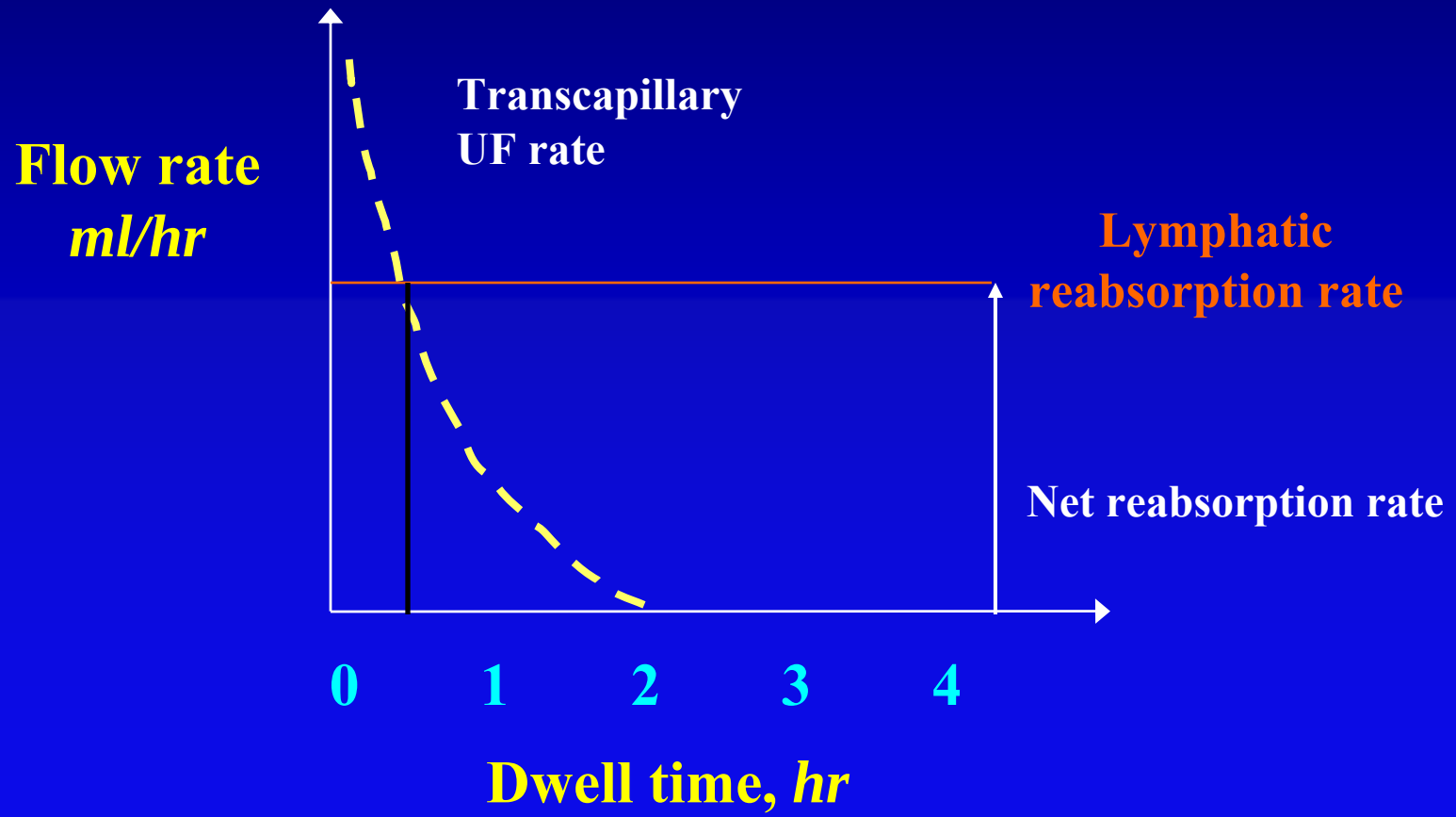
Net UF and Lymphatic Reabsorption Rates in a High Transporter



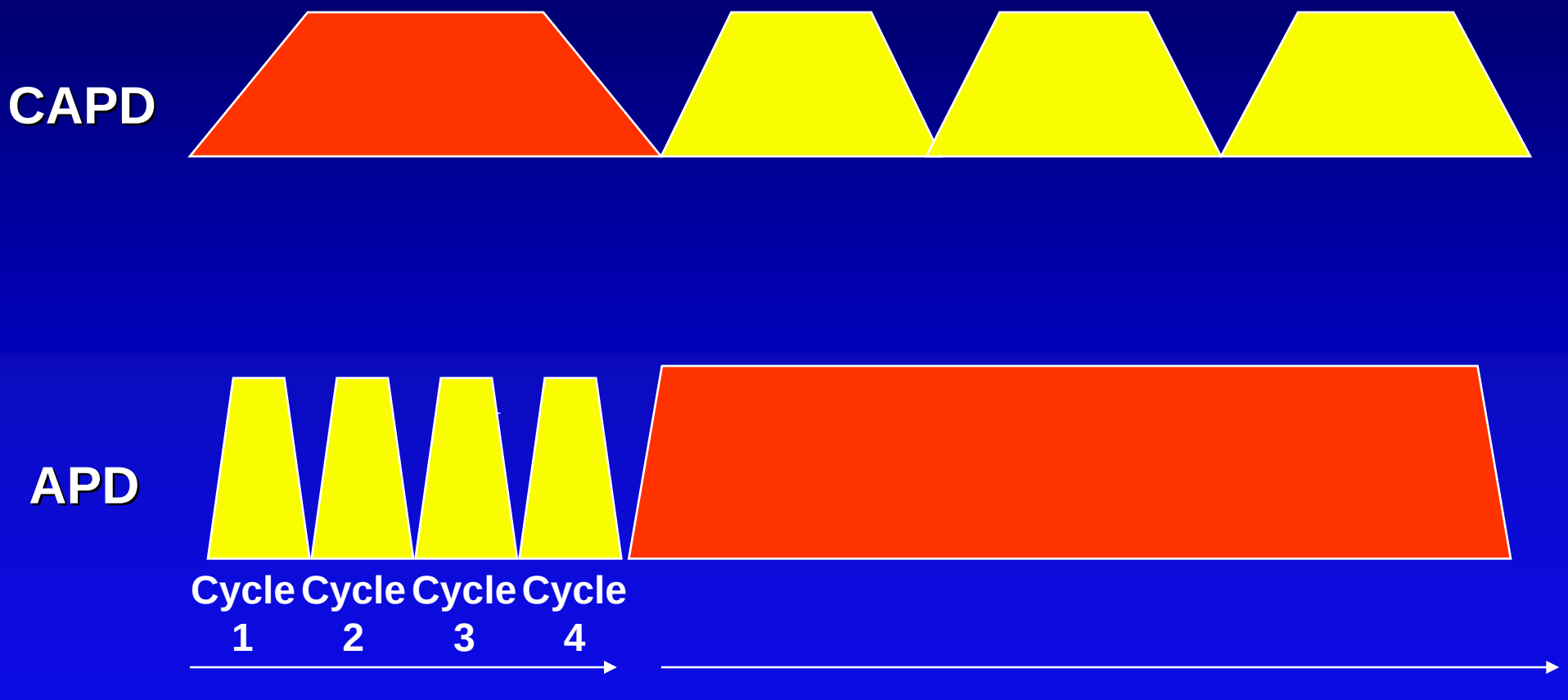
Ultrafiltration Profile in a Patient with High Lymphatic Reabsorption Rate



Net UF in a High Transporter with Increased Lymphatic Reabsorption



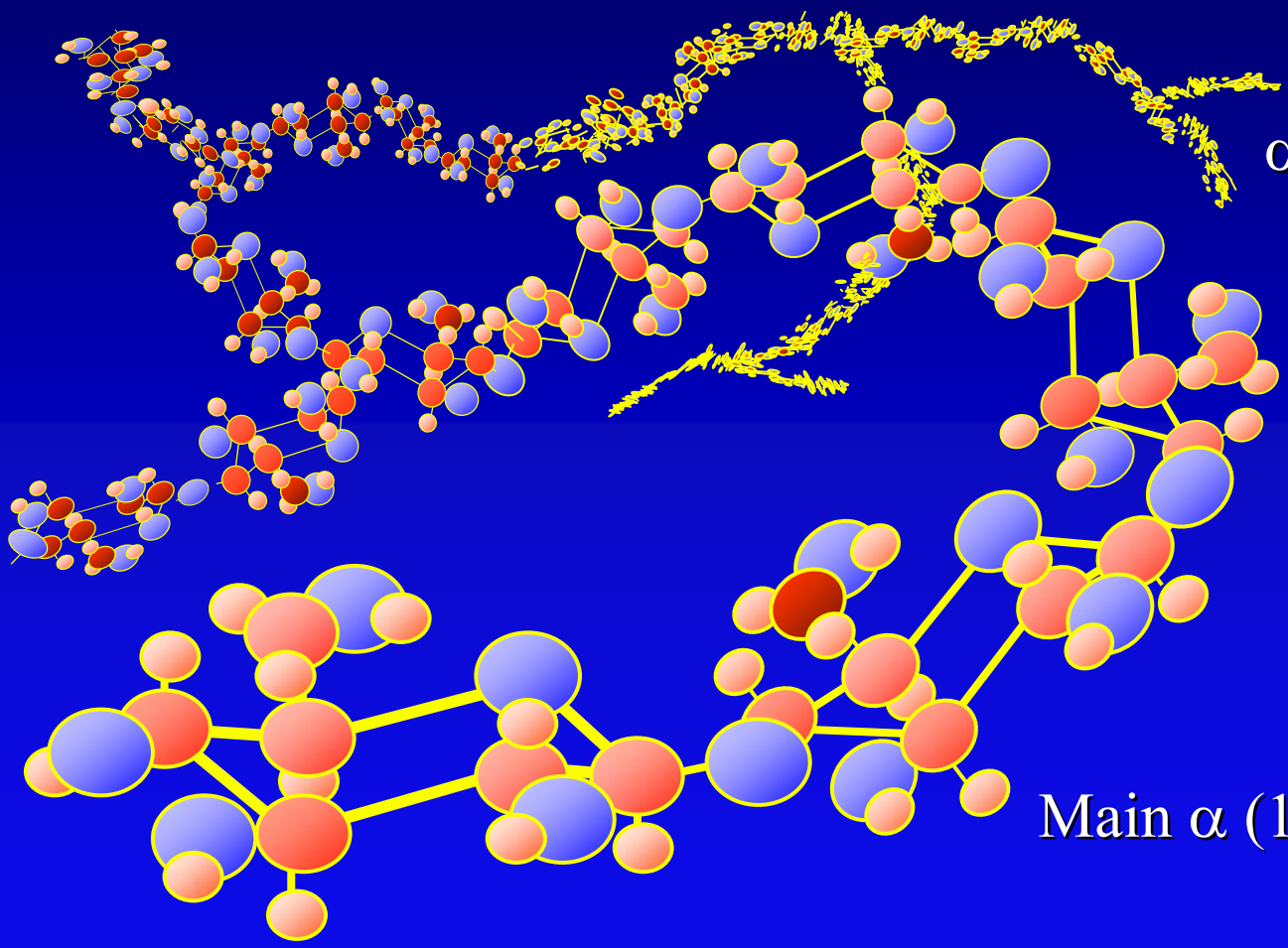
Temporal Profiles of CAPD and APD Prescriptions



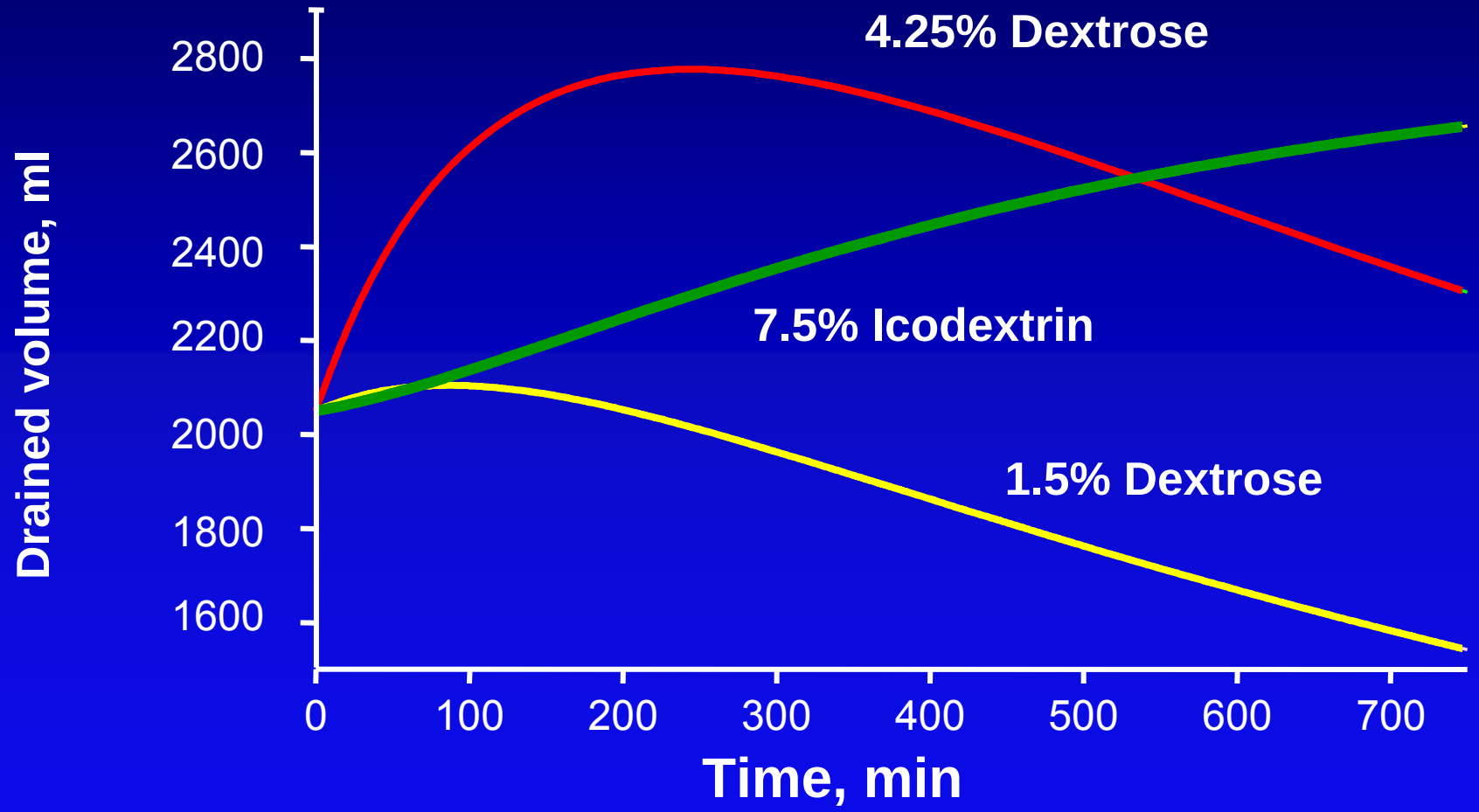
Features of the Alternative Osmotic Agent Icodextrin

- Glucose polymer with average MW around 16,000 Da.
- Effects ultrafiltration through the numerous small intercellular pores (reflection coefficient = 1.0).

Structure of Icodextrin

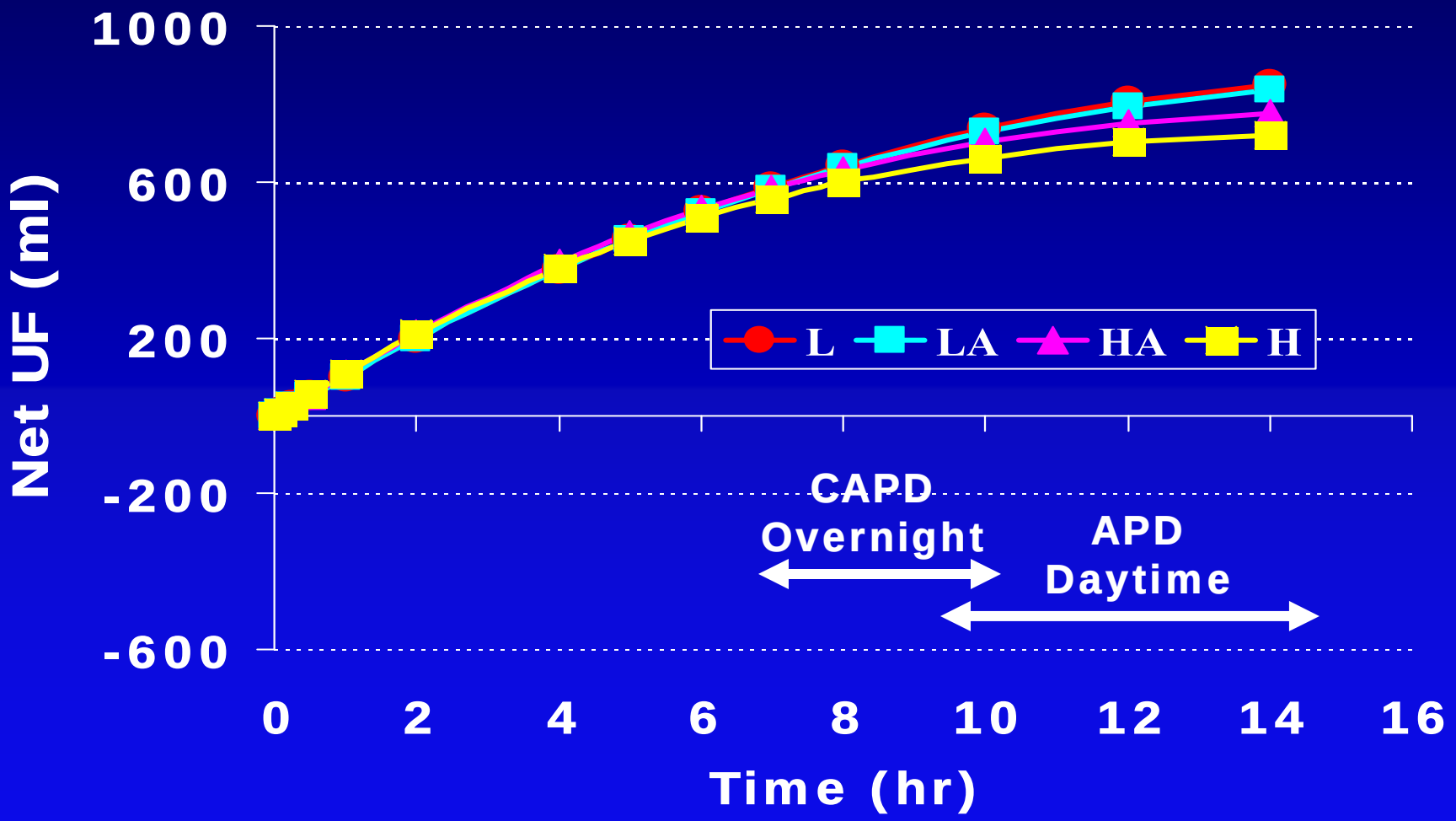


Temporal Profile of Ultrafiltration by Osmotic Agent



Rippe and Levin. Kid Int 57: 2546, 2000

Temporal Profile: Icodextrin



Composition of Icodextrin

	Standard	Icodextrin
Dextrose (g/dL)	**1.5, 2.5, 4.25**	---
Icodextrin (g/dL)	---	**7.5**
Sodium (mEq/L)	132.0	132.0
Chloride (mEq/L)	96.0	96.0
Calcium (mEq/L)	3.5	3.5
Magnesium (mEq/L)	0.5	0.5
Lactate (mEq/L)	40.0	40.0
Osmolality (mOsm/kg)	**346-485**	**282**
pH	5.2	5.2

Key Determinants of Average UF Rate

- Gradient of osmotic agent
- Average reflection coefficient of osmotic agent for small pores and for aquaporins
- Total pore area for small pores and aquaporins

Reflection Coefficients

Large Pores (radius 250 Ang; 3% of pore area)

Glucose 0

Icodextrin 0

Small Pore (radius 40-50 Ang; 95% of pore area)

Glucose 0.05

Icodextrin 1.0

Aquaporins (3-5 Ang; 2% of pore area)

Glucose 1.0

Icodextrin 1.0

Osmotic Gradients at Exchange Initiation

- 3.86% glucose = (38,600 mg/L) / 180 mg/mOsm = 214 mOsm/L in dialysate (d)
  - d-p = 214 - 5 = 209 mOsm/L gradient
- 7.5% icodextrin = 75000 mg/L / 16,000 mg/mOsm = 4.7 mOsm/L in dialysate (d)
  - d-p = 4.7 – 0 = 4.7 mOsm/L gradient

Osmotic Pressure – Small Pores

Osmotic Pressure with glucose solution (mm Hg) = [0.05($gluc_d$ – $gluc_p$) + 0.05 (Na_d – Na_p) +0.0 ($urea_d$ - $urea_p$) + 0.05 (Cl_d – Cl_p) + etc] x [17mm Hg/ mosm/L]

*for icodextrin add 1.0(ico_d – ico_p) within first bracket

Osmotic Pressure – Aquaporins

For both glucose and icodextrin solutions use the same equation as on the previous slide but use a reflection coefficient of 1.0 for each.

How Glucose Induces UF Across Aquaporins

- The reflection coefficient is 1.0
- The effective gradient is high (209 mOsm/L)
- The initial osmotic pressure is extremely high (209 x 17 = 3553 mm Hg).
- The above yields UF despite the very low pore area (2%).

Why Icodextrin Yields Only Minimal UF Via Aquaporins

- Although the reflection coefficient is high (1.0), the effective gradient is very low (4.7 mOsm/L).
- Initial osmotic pressure is low (4.7 x 17 = 80 mm Hg).
- Pore area is low (2%).
- Minimal UF rate does not decrease dialysate [Na] hence, no sieving.

Why Icodextrin Solutions Yield UF Even with Osmolality Less than that of Plasma

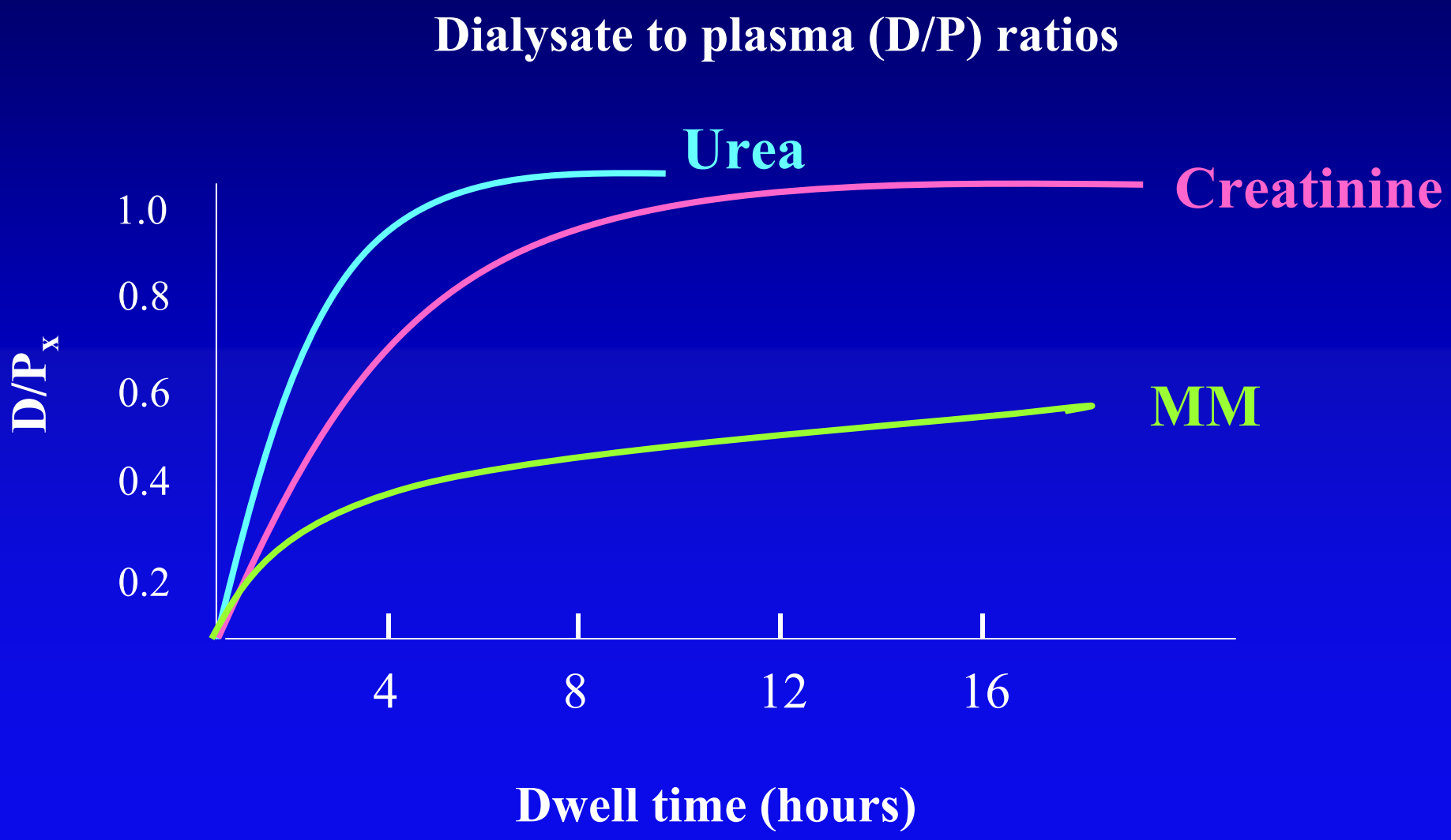
- The effective osmotic gradient due to icodextrin is more positive than the sums of any negative effective gradients for other solutes yielding a positive effective osmotic gradient.
- This results from the very low reflection coefficients for sodium, chloride, urea, etc.
- And this effect is exerted over a large pore area (97%).

Possible Clinical Ramifications of Retained MMW Solutes in Uremia

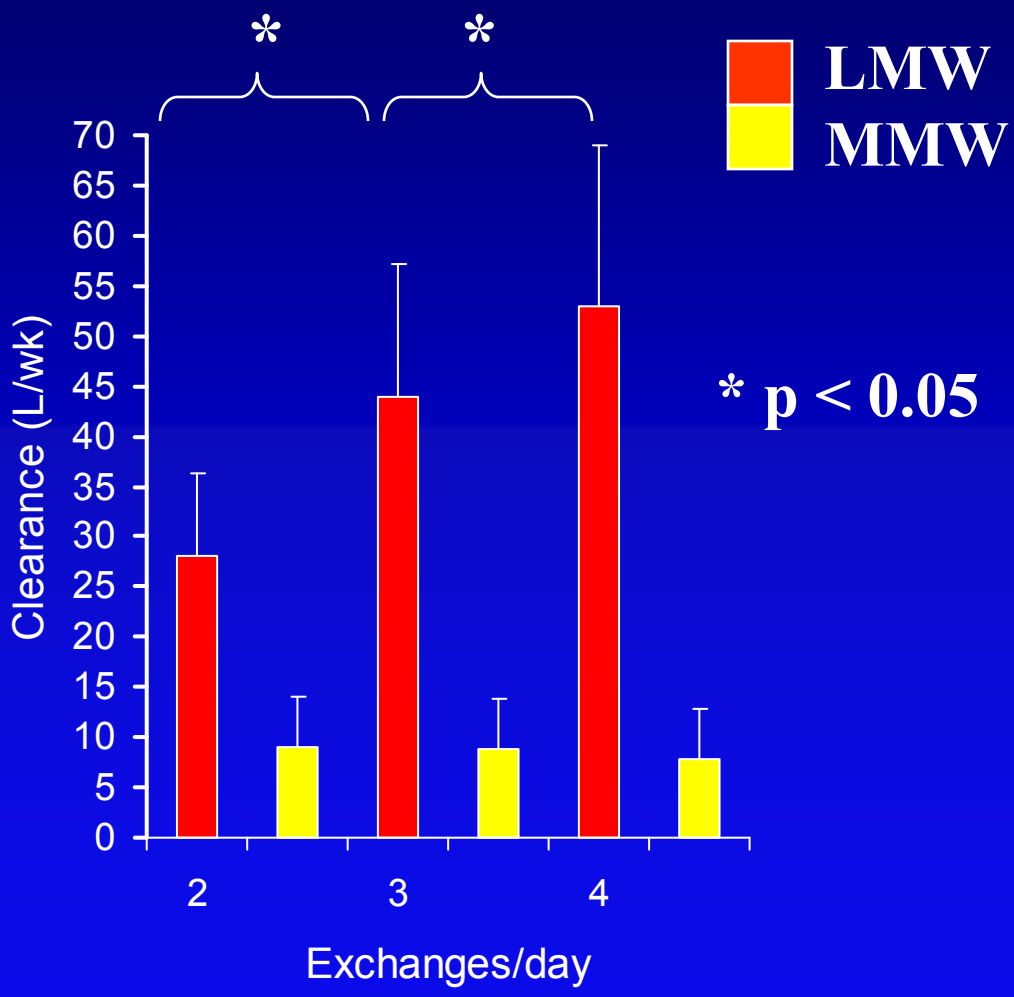
Probably related to some long term complications of uremia:

- Dialysis acquired amyloidosis
- Accelerated CV risk profile
- Uremic platelet dysfunction
- Immunodeficiency

Diffusion Curves for Solutes of Varying Size



Dissociation Between Clearances of Low and Middle Molecular Weight Solutes

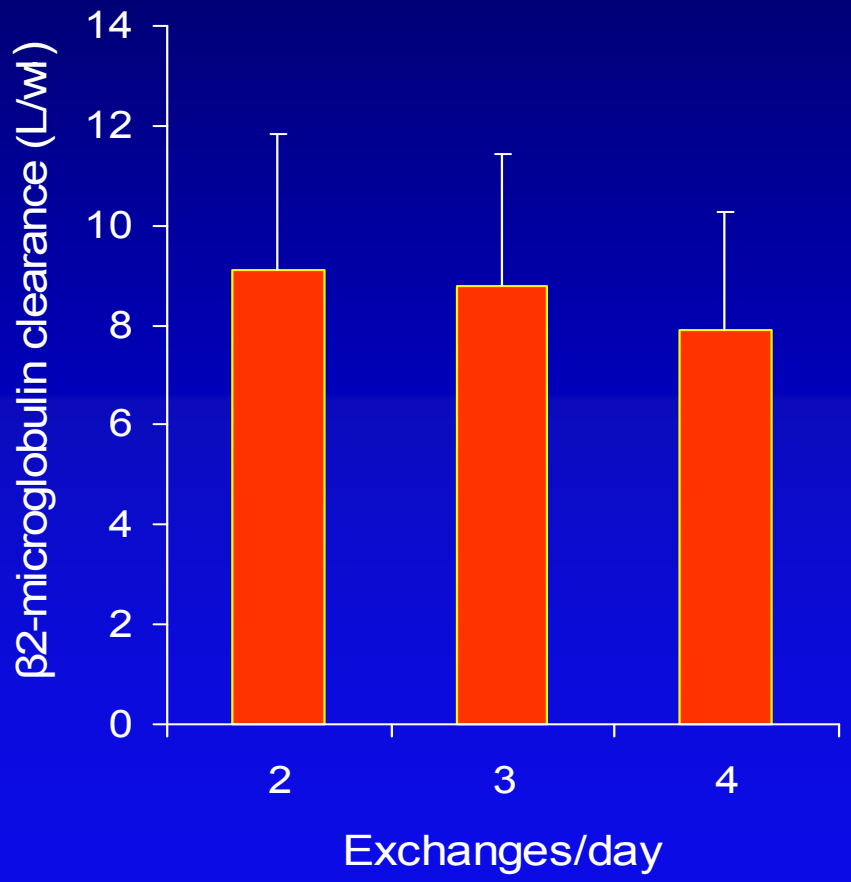


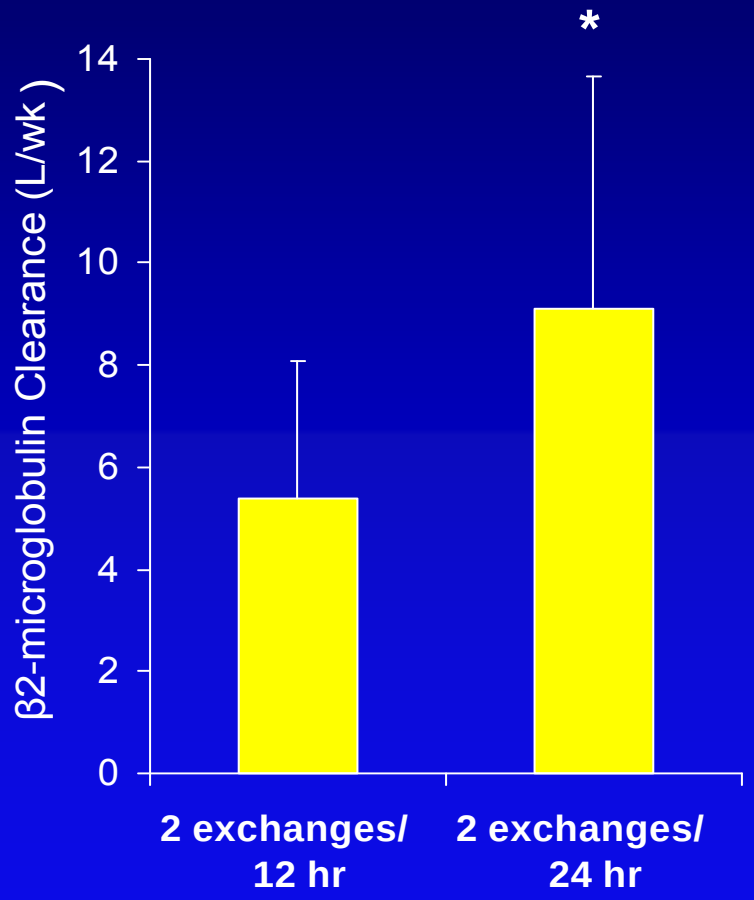
* $p < 0.05$

- As the number of exchanges/24 hours increases LMW solute clearance improves
- As the number of exchanges/24 hours increases MMW solute clearance does **NOT** improve

Kim et al. Perit Dial Int 21: 462, 2001

Middle Molecule Clearance is Dwell Time Dependent

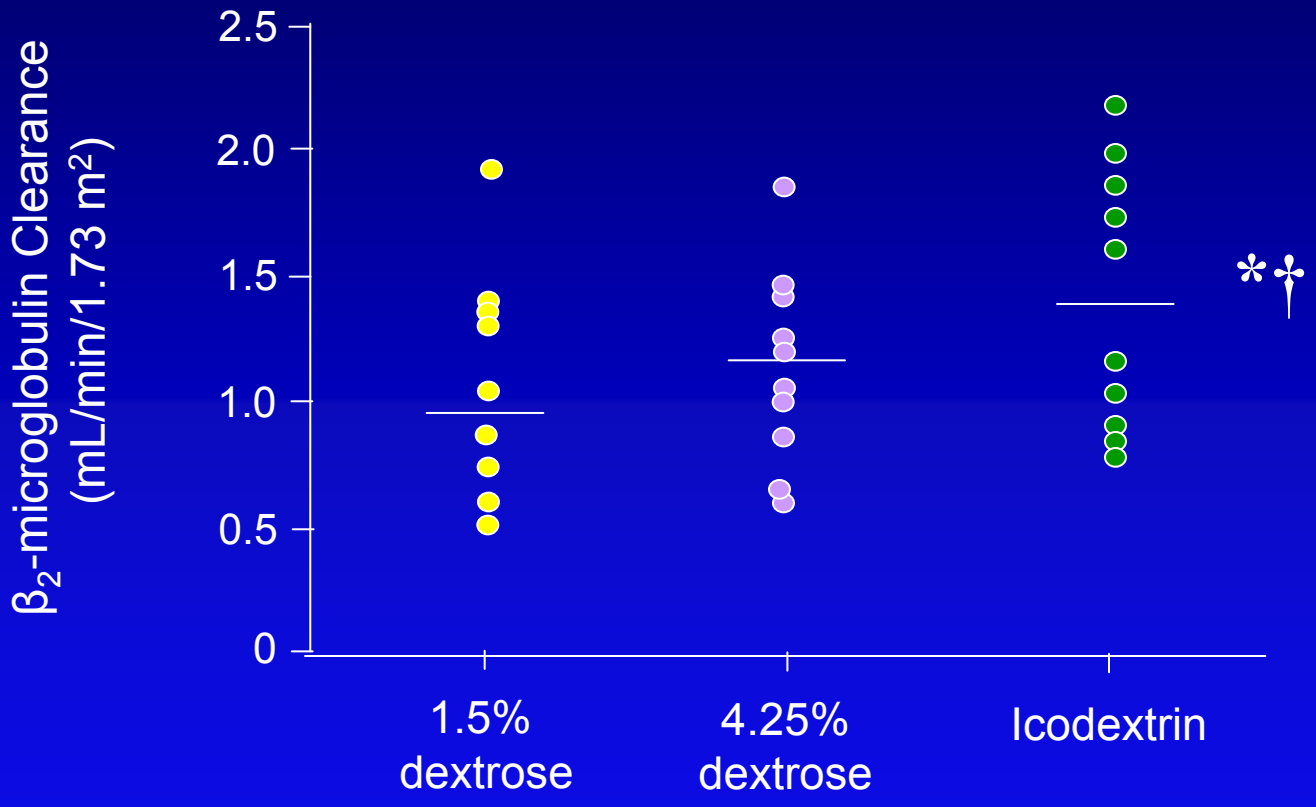




*p <.05 vs 2 exchanges/12 hr

Kim et al. Perit Dial Int 21: 462, 2001

β_2-Microglobulin Clearance (4 hour dwell): Icodextrin *vs.* Dextrose



*p = 0.008, icodextrin *vs.* 1.5% dextrose

†p = 0.01, icodextrin *vs.* 4.25% dextrose

Ho- dac- Pannekeet et al. Kid Int 50: 979, 1996

Outline

- Peritoneal cavity as a dialysis system
- Models of peritoneal transport
- Physiology of peritoneal transport
  - Inverse relationship between solute transport and ultrafiltration
- Kinetics of peritoneal transport
- Synthesis & Application
- Middle Molecules

THANK YOU

Question #1

- A patient is admitted in pulmonary edema and multiple rapid PD exchanges with 4.25% dextrose are performed. Which of the following may ensue as a consequence of sodium sieving?
  - A. Hyponatremia due to rapid water transport from dialysate to plasma via aquaporins.
  - B.Hypernatremia due to rapid sodium entry from dialysate to plasma via the small pores.
  - C. Hypernatremia due to rapid water transport from plasma to dialysate via aquaporins.
  - D. Hypokalemia due to rapid Na/ K exchange by Na/K ATPase in the mesothelium.

Question #1: Answer

- The correct answer is “C”. When doing very hypertonic exchanges, e.g. with 4.25%, free water moves via the aquaporins from blood into dialysate, leaving behind Na in excess of water. If one performs multiple such exchanges in short order this may culminate in hypernatremia.

Question #2

- A patient has a 4 hour D/Pcr of 0.88 and D/D0 glucose of 0.35. Which of the following best describes the anticipated clinical findings using 1.5% dextrose dialysate and CAPD?
  - A. Good solute clearance and good ultrafiltration.
  - B. Poor solute clearance and good ultrafiltration.
  - C. Poor solute clearance and poor ultrafiltration.
  - D. Good solute clearance and poor ultrafiltration.

Question #2: Answer

- The correct answer is “D”. The 4 hour D/Pcr of 0.88 and D/D0 glucose of 0.35 are indicative of a very rapid transporter. This individual would therefore be expected to have good solute clearance. However, s/he would dissipate the glucose- induced osmotic gradient very rapidly and would therefore be likely to absorb fluid from the abdominal cavity resulting in poor ultrafiltration