Osmotic Conductance to Glucose: What does it mean?

B. Bammens, MD, PhD

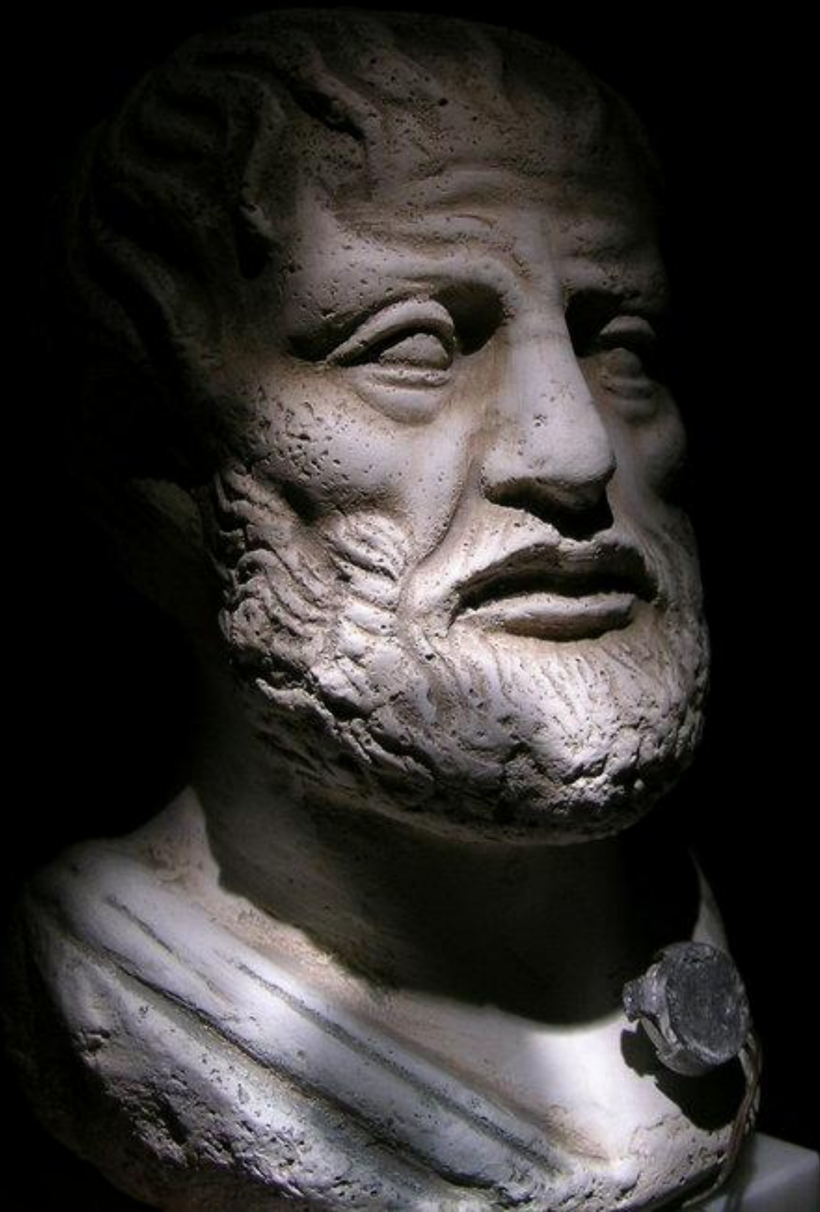
Brussels, May 22 2014

UZ LEUVEN BELGIUM

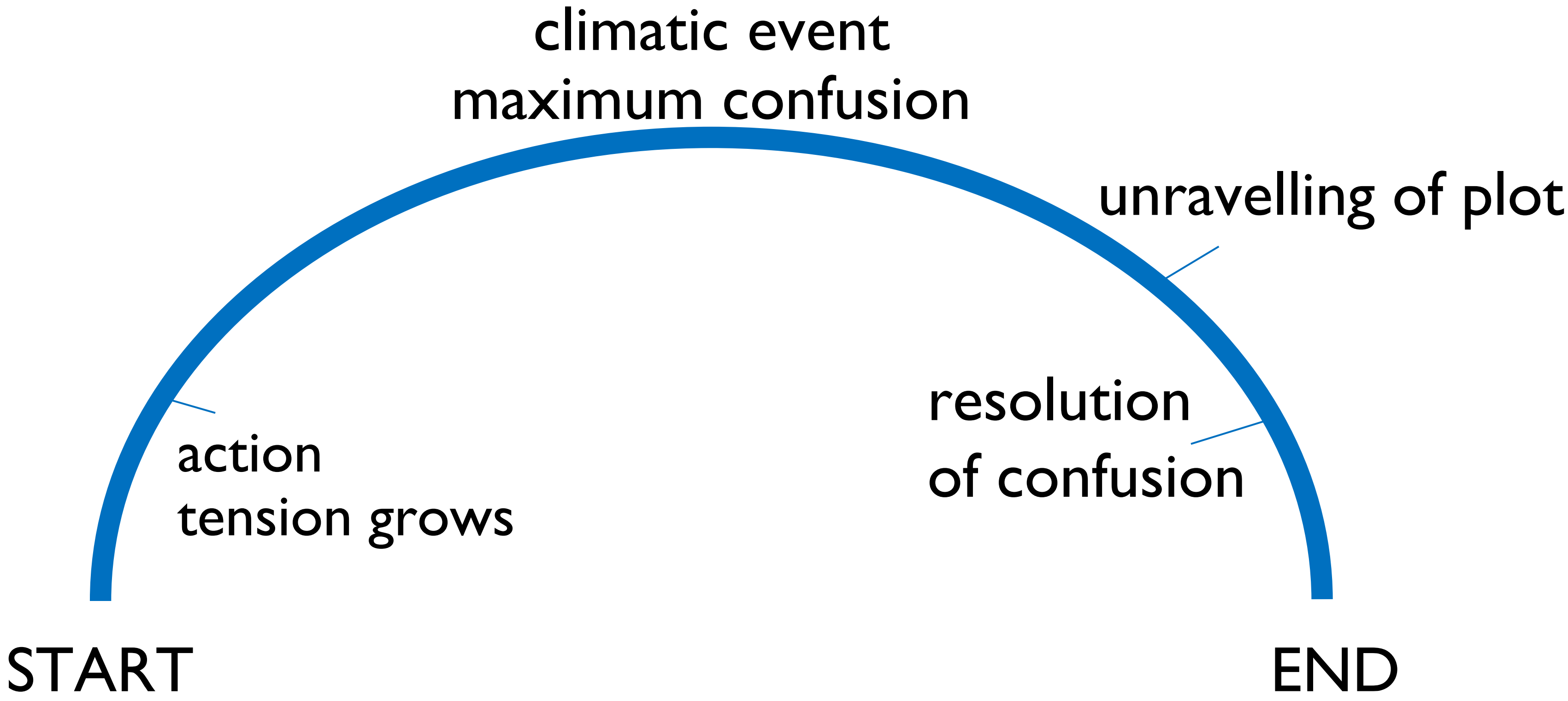
self-care dialysis symposium

2nd self-care dialysis symposium

Aristoteles
384-322 B.C.

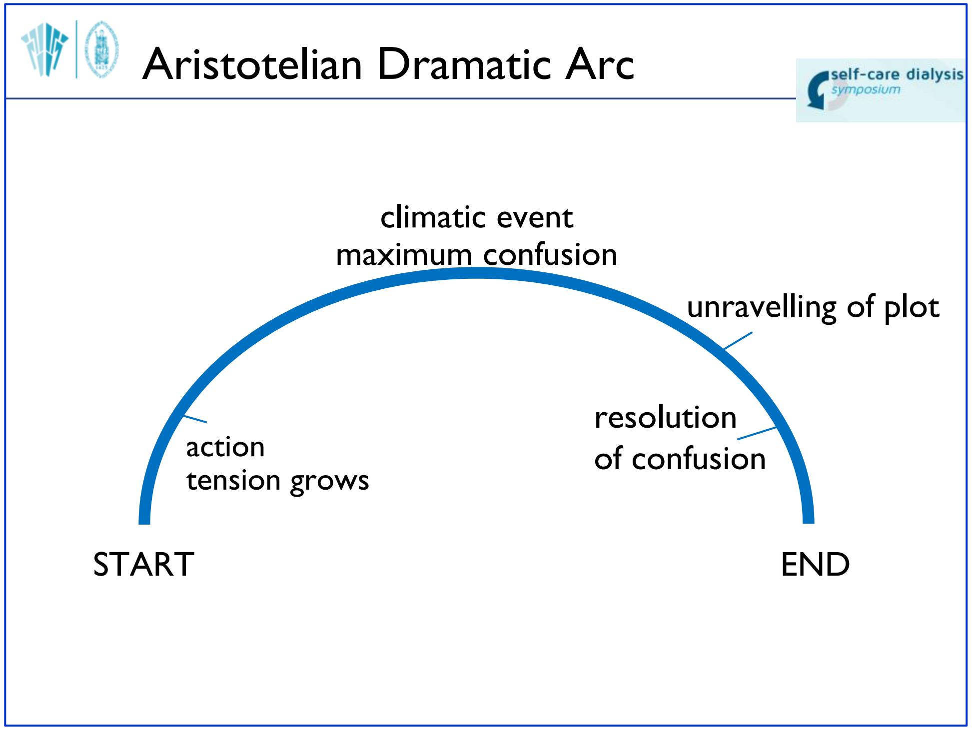


Aristotelian Dramatic Arc



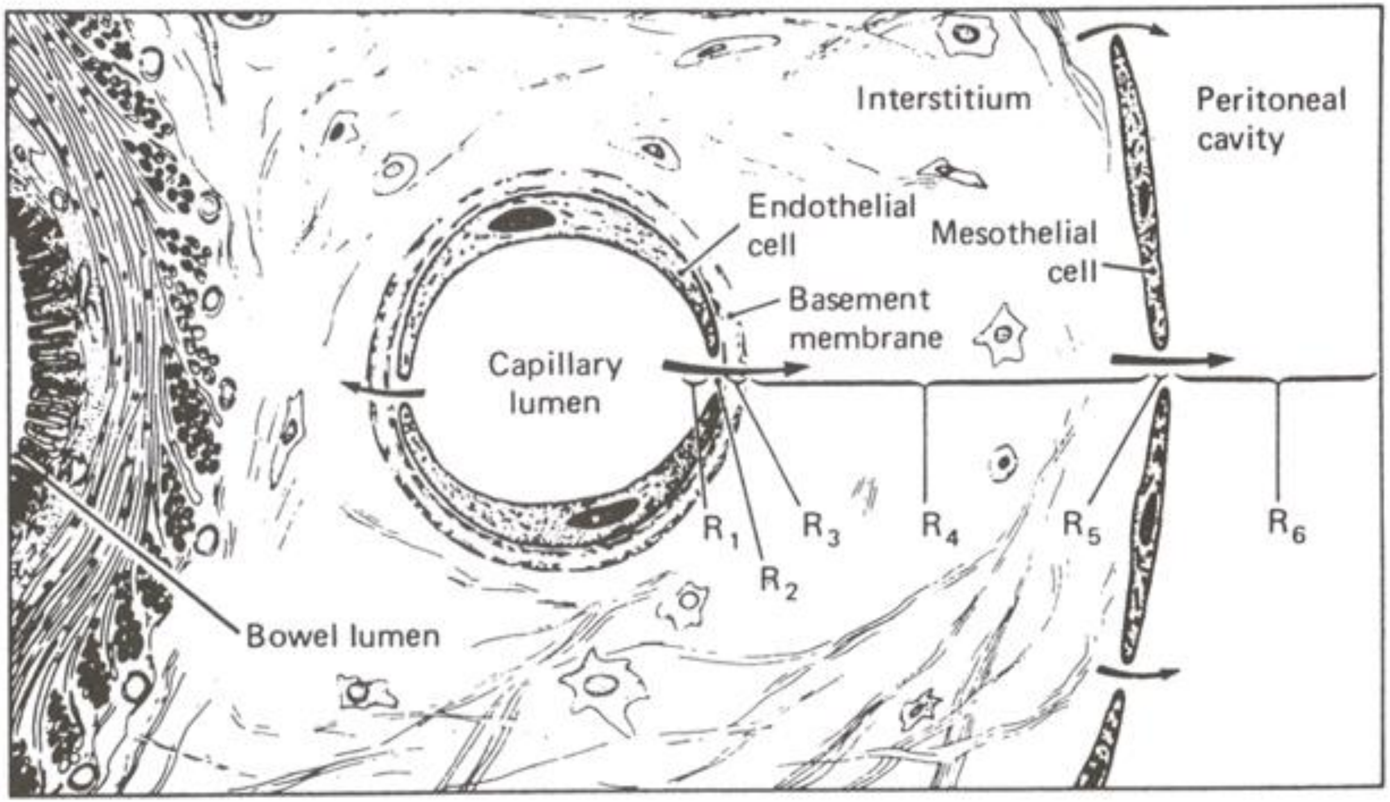
Osmotic Conductance to Glucose

- Essential peritoneal membrane physiology
- Please welcome: OCG!
- OCG: what does it mean?



'6 barriers for transport'

Stagnant layers at mesothelial and capillary side: not relevant
Mesothelial cell layer: not relevant
Interstitial tissue: (minor) diffusive resistance
Capillary wall: most important restriction barrier



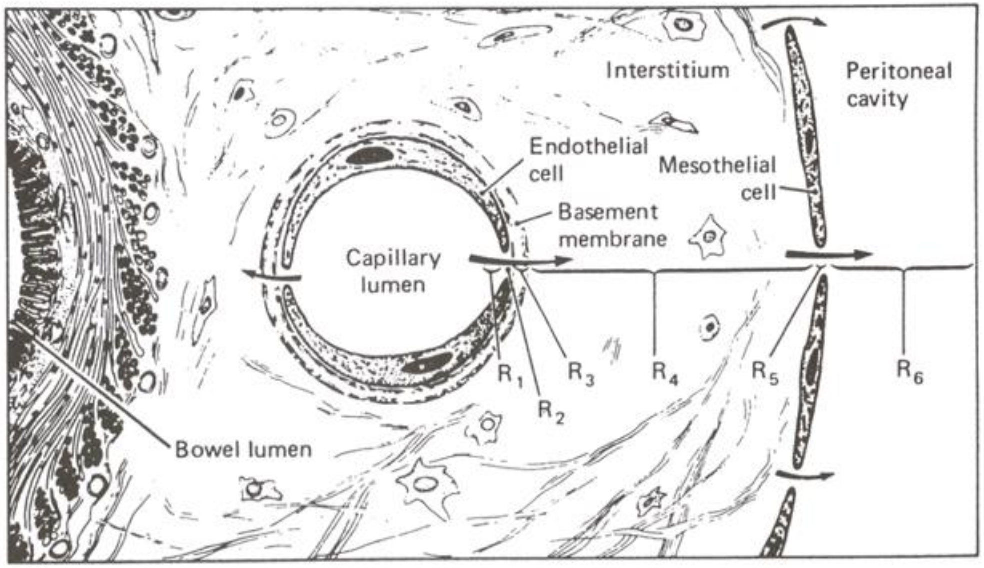
Nolph et al. Kidney Int 18 (Suppl 20): S111-S116, 1980
Flessner et al. J Am Soc Nephrol 2: 122-135, 1991

‘2D membrane with pores’

self-care dialysis symposium

Capillary wall is the most important restriction barrier and determines the peritoneal membrane’s size-selectivity through a system of pores

→ the “PORE THEORIES”



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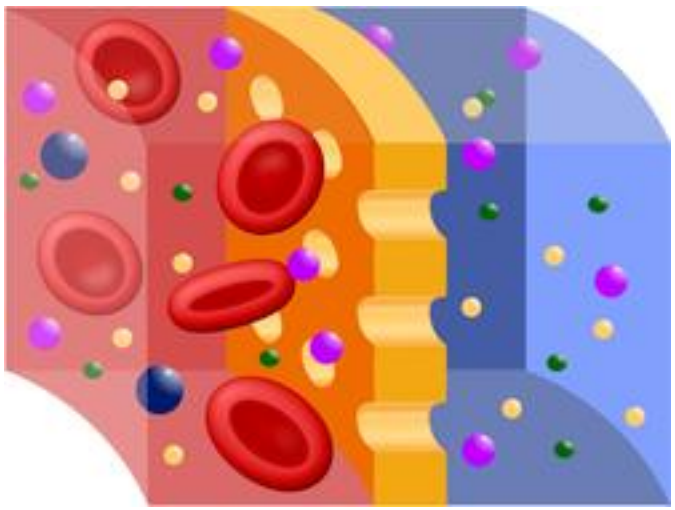
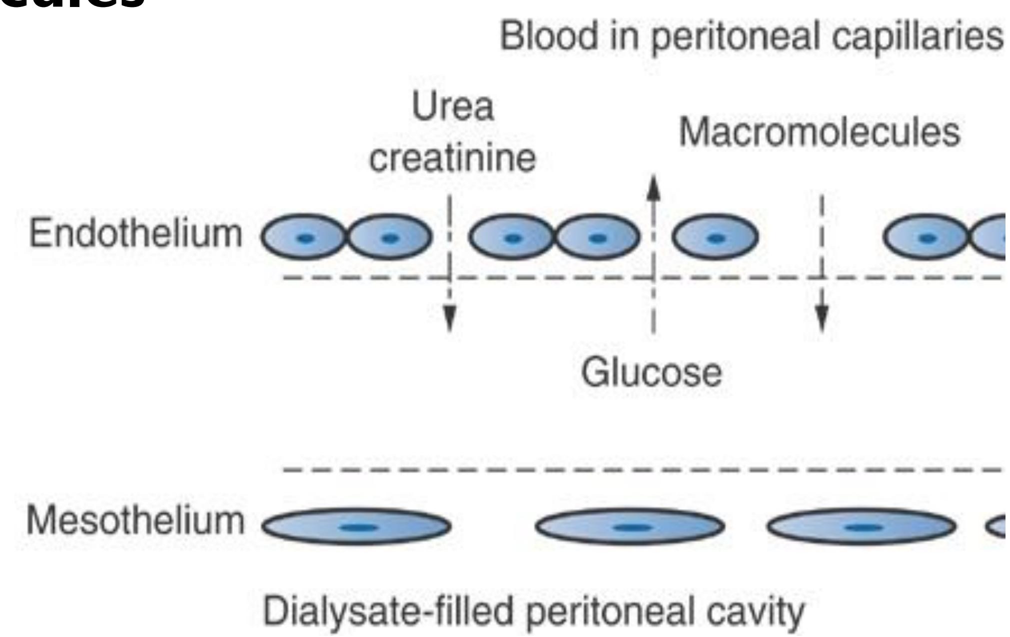


'Old' theory: TWO pores

Small pores with constant radius 40-50Å (majority)
for transport of low molecular weight solutes

Large pores with various radii, average > 150Å (minority, less than 0.1% of total pore count)
for transport of macromolecules

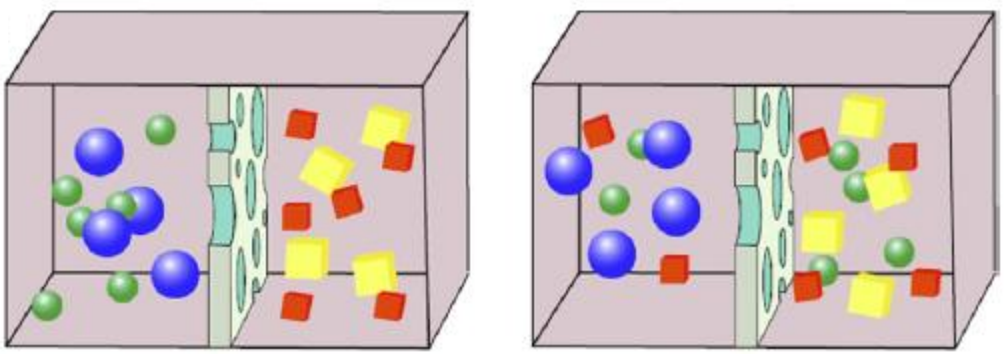


'Old' theory: TWO pores

The two-pore theory perfectly explains the <u>diffusive transport</u> of molecules.

DIFFUSION

movement of solutes along their concentration gradient



Bammens Semin Nephrol 31: 127-137, 2011

Diffusive transport

$$J_s = \frac{D_f}{\Delta x} . A . \Delta C$$

(Fick's first law of diffusion)

diffusive permeability (membrane- and solute-specific)

Diffusive transport

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diffusive permeability (membrane- and solute-specific)

surface area (membrane-specific)

Diffusive transport

$$J_s = \frac{D_f}{\Delta x}.A.\Delta C$$

(Fick's first law of diffusion)

diffusive permeability (membrane- and solute-specific)

surface area (membrane-specific)

concentration difference between plasma and dialysate

Diffusive transport

$$J_s = \frac{D_f}{\Delta x} . A . \Delta C$$

(Fick's first law of diffusion)

diffusive permeability (membrane- and solute-specific)

surface area (membrane-specific)

concentration di … sma and dialysate

mass transfer area coefficient (MTAC)

Diffusive transport

$$J_s = \frac{D_f}{\Delta x} . A . \Delta C$$ (Fick's first law of diffusion)

$$J_s = MTAC . \Delta C$$

Transport of small molecules up to MW of β_2M (11,8 kDa) NOT limited by size of (large) pores

⇩

MTAC for a given solute ONLY determined by effective vascular peritoneal surface area (number of pores)

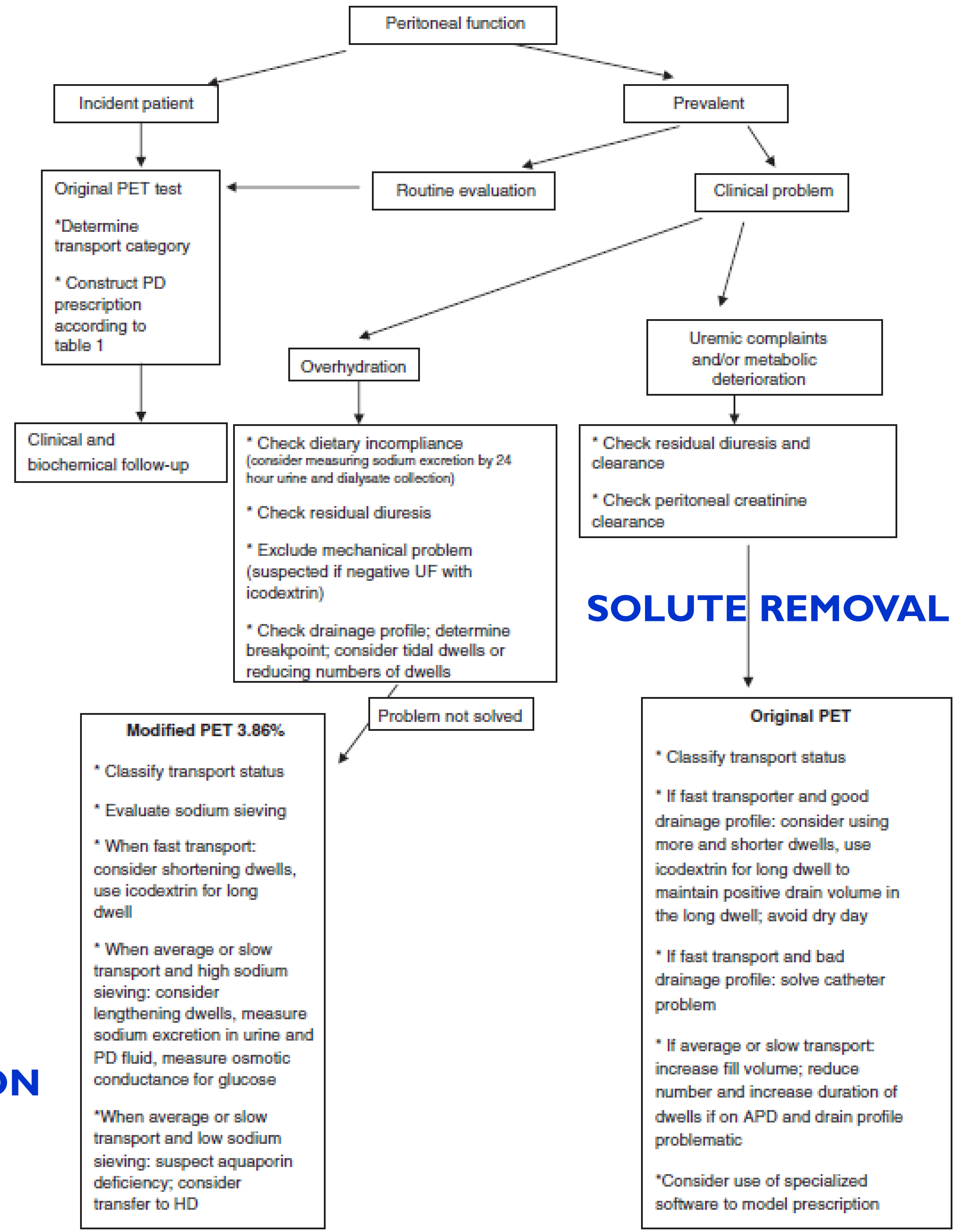
‘Old’ theory: TWO pores

The two-pore theory perfectly explains the diffusive transport of molecules.

However, it does <u>not</u> explain <u>all</u> aspects of the convective transport of molecules and ultrafiltration.

SOLUTE REMOVAL

ULTRAFILTRATION



Caring for Australasians with Renal Impairment

Canadian Society of Nephrology/ Société Canadienne De Néphrologie CSN/SCN

National Kidney Foundation™

The Renal Association founded 1950

International Society for Peritoneal Dialysis

European Renal Association – European Dialysis and Transplant Association

Registered Charity No. 1060134

ULTRAFILTRATION

European Renal Best Practice

Van Biesen et al. Nephrol Dial Transplant 25: 2052-2062, 2010

‘Old’ theory: TWO pores

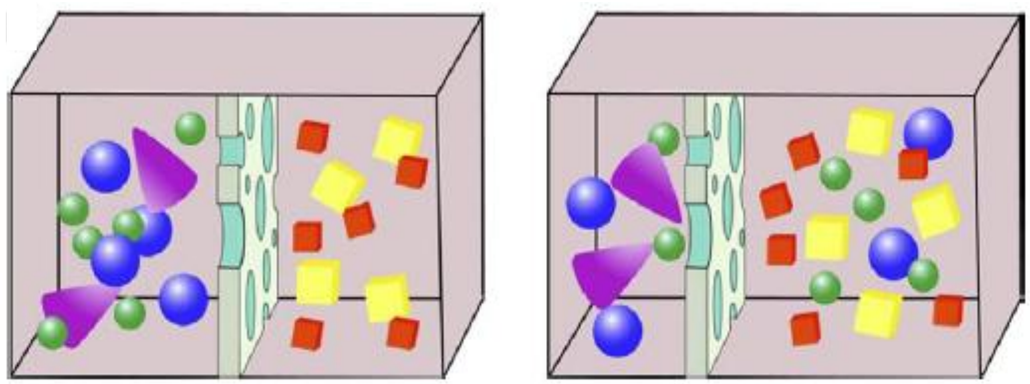
However, it does <u>not</u> explain <u>all</u> aspects of the convective transport of molecules and ultrafiltration.

CONVECTION

movement of solutes along with fluid as it moves across the membrane (solvent drag)

Bammens Semin Nephrol 31: 127-137, 2011

Convective transport



Bammens Semin Nephrol 31: 127-137, 2011

Convective transport

$$J_s = J_v.\bar{C}.(1-\sigma)$$

Convective transport

$$J_s = J_v . \bar{C} . (1 - \sigma)$$

water flux (membrane-specific)

Convective transport

$$J_s = J_v \cdot \bar{C} \cdot (1 - \sigma)$$

water flux (membrane-specific)

mean solute concentration in the membrane (P+D)/2

Convective transport

$$J_s = J_v . \bar{C} . (1 - \sigma)$$

water flux (membrane-specific)

mean solute concentration in the membrane (P+D)/2

Staverman's reflection coefficient
= *how difficult it is for a solute to be transported by solvent drag across a semi-permeable membrane*
(membrane- and solute-specific)

Convective transport

σ Staverman's reflection coefficient

= how difficult it is for a solute to be transported by solvent drag across a semi-permeable membrane

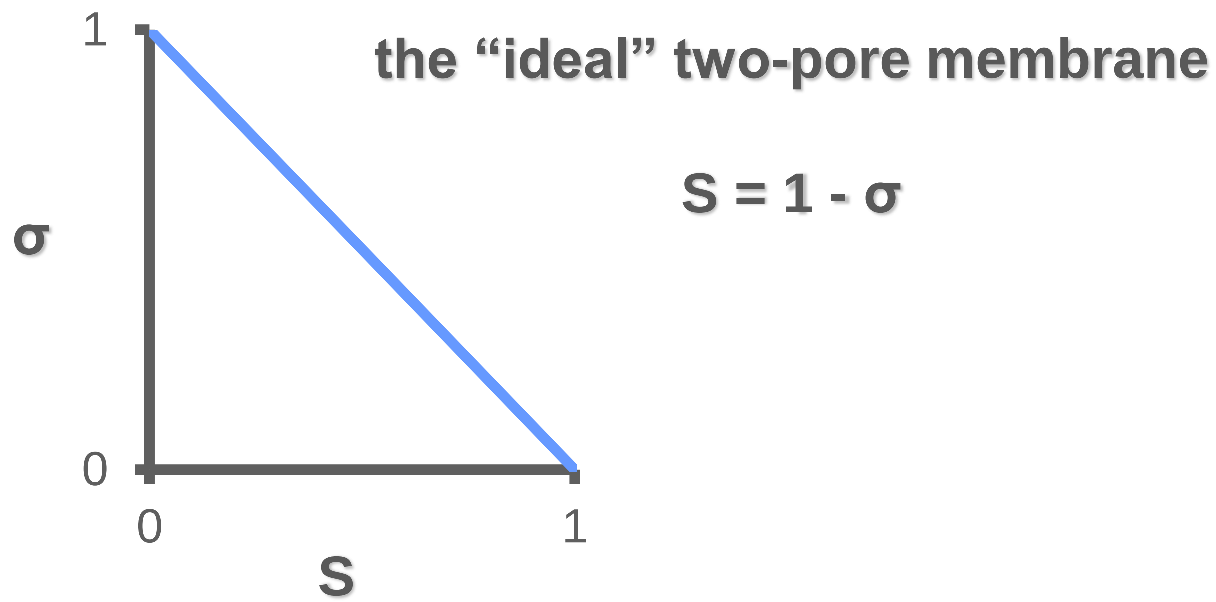
⇕

S sieving coefficient

= how easy it is for a solute to be transported by solvent drag across a semi-permeable membrane

Convective transport

For a semi-permeable membrane, S and σ are expected to be perfectly interchangeable concepts!



Convective transport

σ Staverman's reflection coefficient

= how difficult it is for a solute to be transported by solvent drag across a semi-permeable membrane

= fraction of maximal osmotic pressure a solute can exert across a semi-permeable membrane

⇕

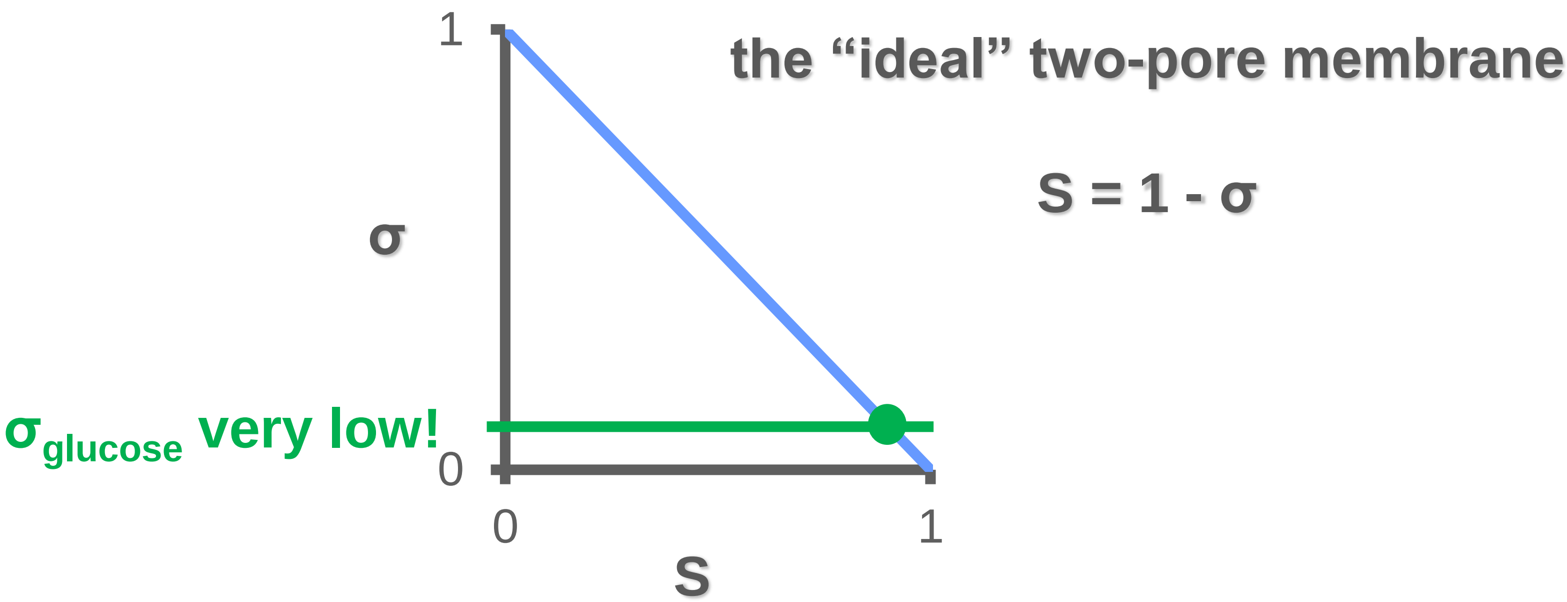
S sieving coefficient

= how easy it is for a solute to be transported by solvent drag across a semi-permeable membrane

= fraction of maximal solute transport by solvent drag across a semi-permeable membrane

Convective transport

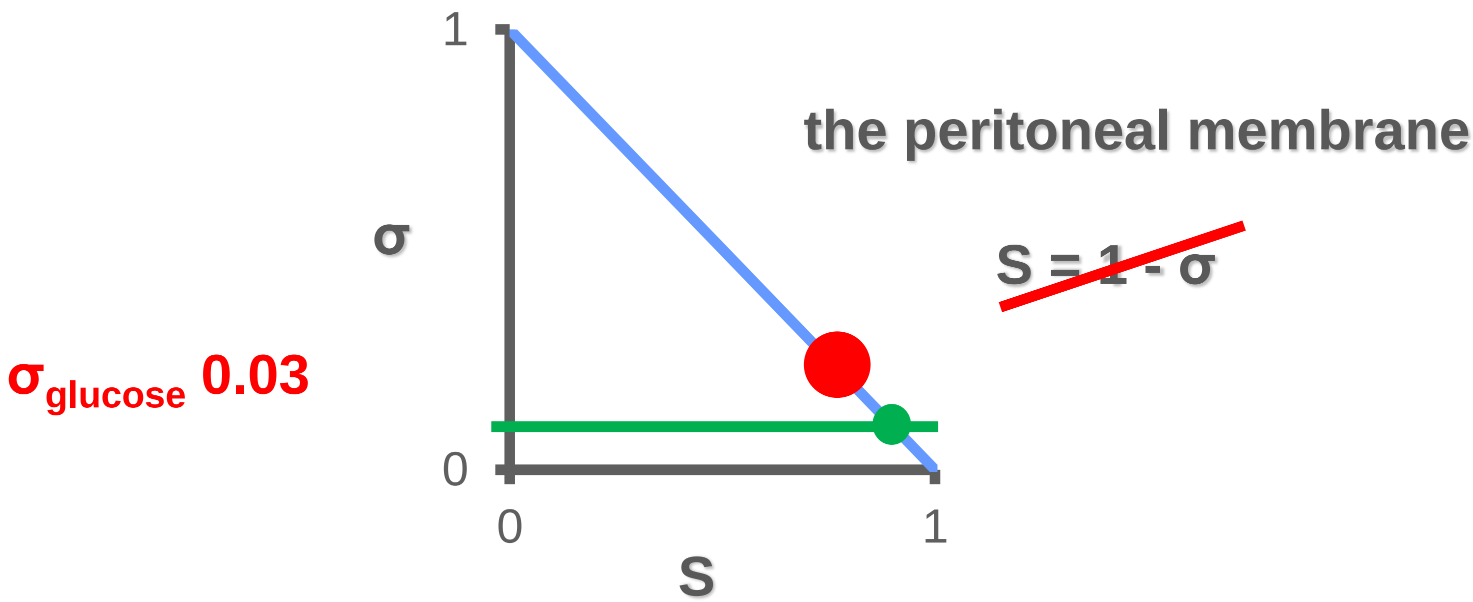
For a semi-permeable membrane, S and σ are expected to be perfectly interchangeable concepts!



Apparent $\sigma_{glucose}$ = higher

For a semi-permeable membrane, S and σ are expected to be perfectly interchangeable concepts!

However, the peritoneal membrane seems not to fulfill this "ideal semi-permeable membrane" criteria.



‘New’ theory: THREE pores

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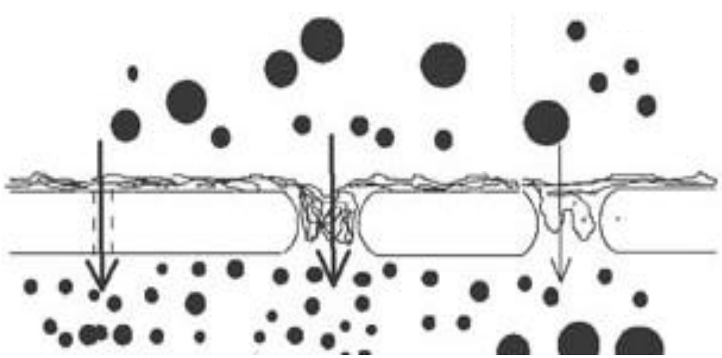
symposium

Small pores with constant radius 40-50Å
Large pores with various radii, average > 150Å

Ultra-small pores with radius 3-5Å

for transport of water only
accounts for 1/2 of transcapillary water transport

(explains good osmotic properties of glucose)



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Ultra-small pores with radius 3-5Å

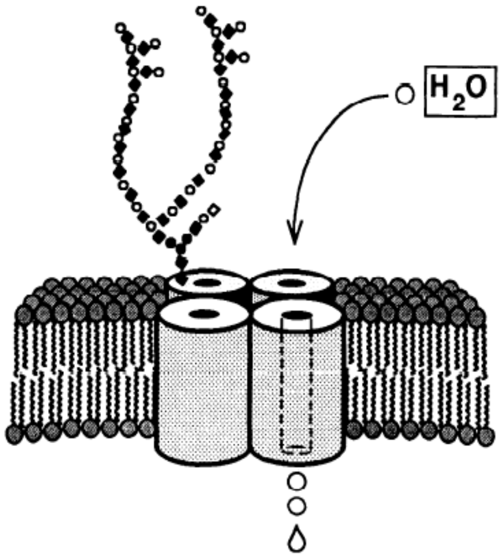
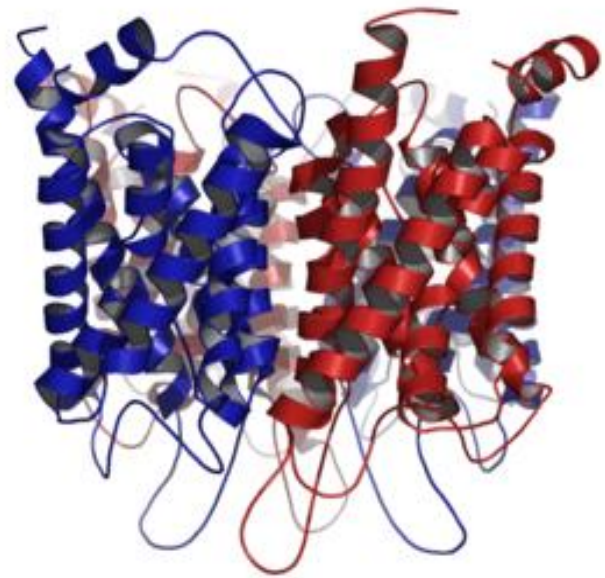


Fig. 1. Schematic model representing CHIP integral membrane protein within the membrane lipid bilayer. Notable features include *1*) homotetrameric complex with 1 subunit bearing a polylactosaminoglycan, *2*) minimal polypeptide mass extending above or below the lipid bilayer, and *3*) possible individual water pore within each subunit.

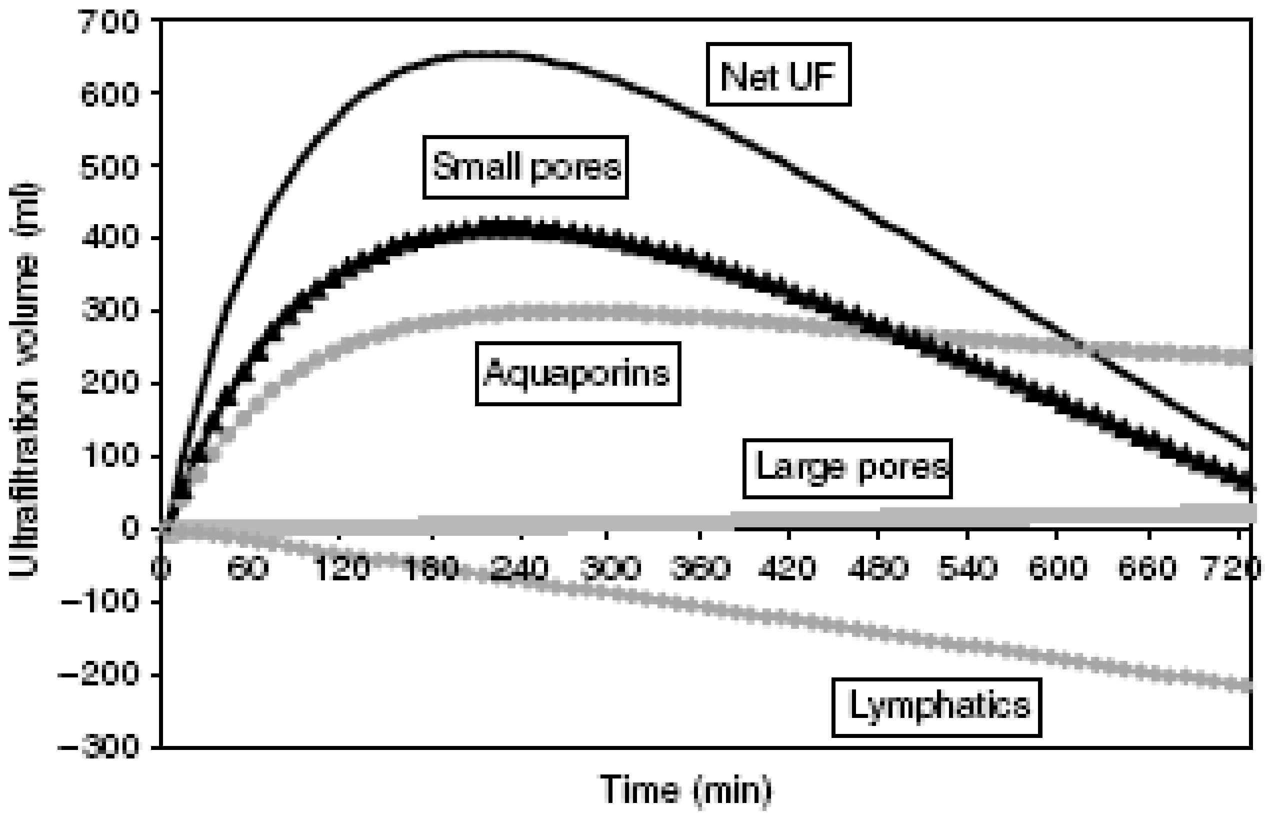
AQUAPORIN-1



Agre et al. Am J Physiol 265: F463-F476, 1993

‘New’ theory: THREE pores

ULTRAFILTRATION



Davies Kidney Int 70 (Suppl 103): 76-83, 2006

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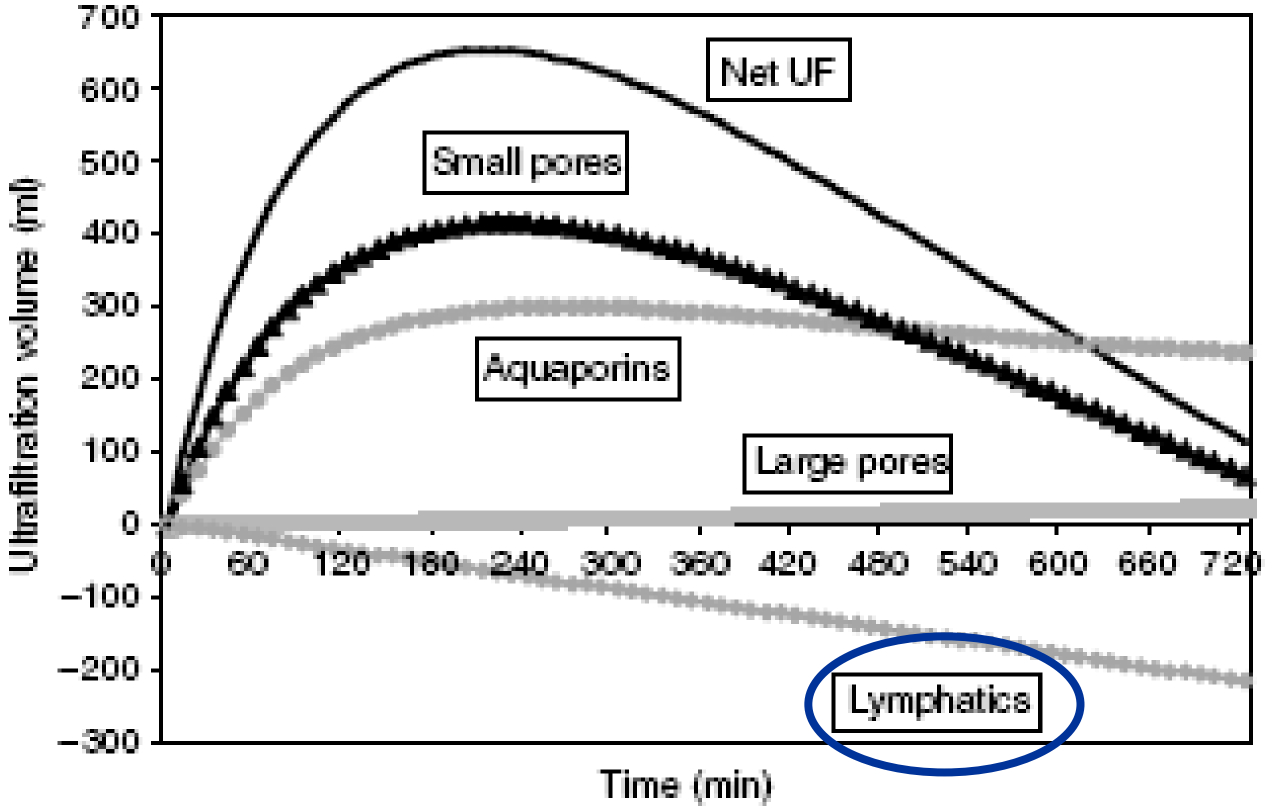

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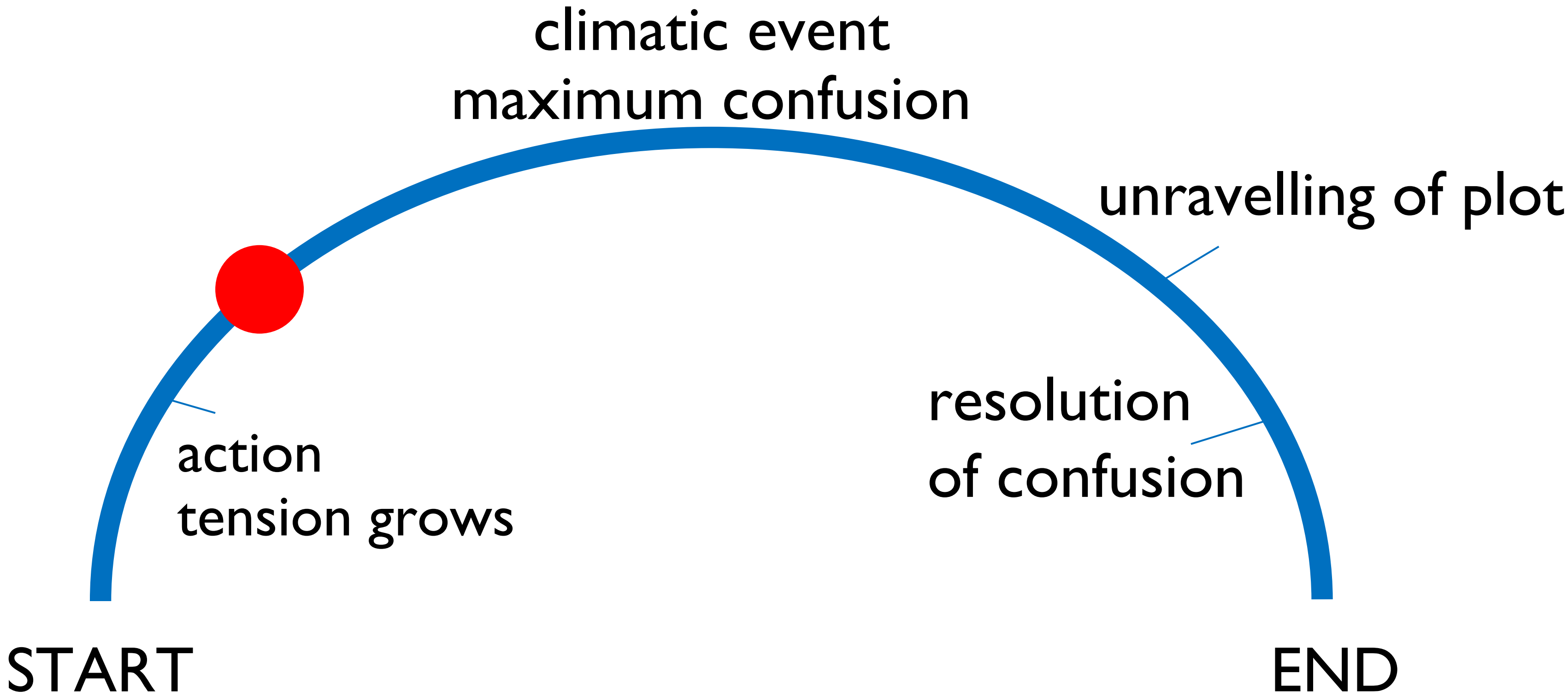
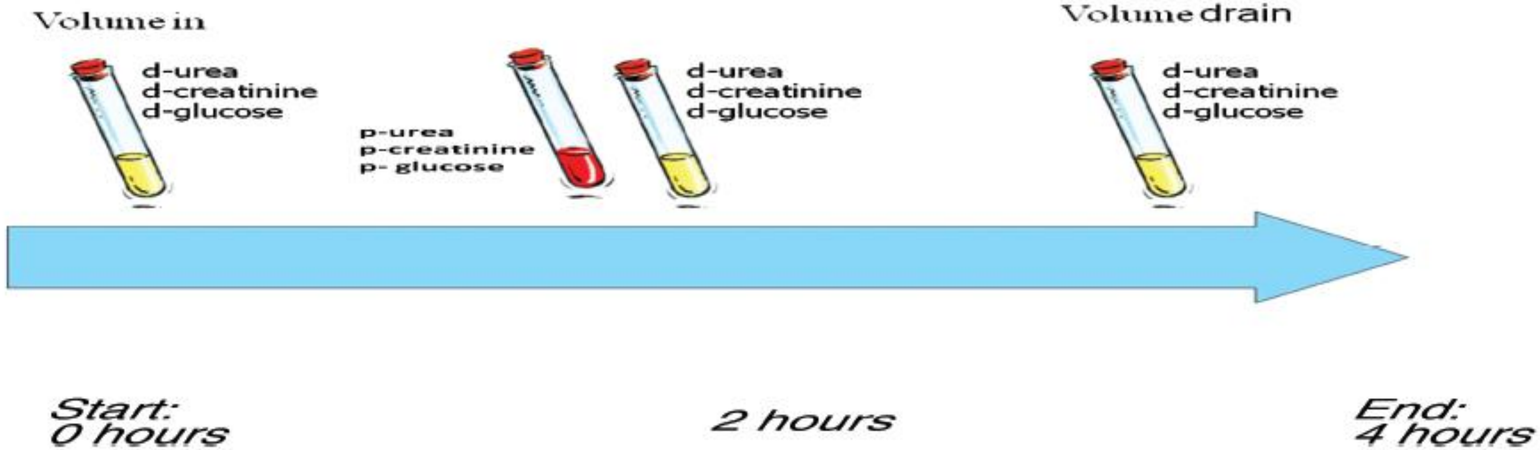
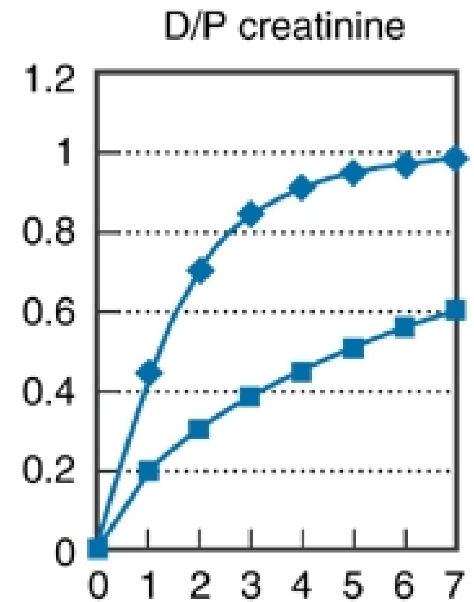


The original 2.27% PET test



SOLUTE TRANSPORT



(D/Pcreatinine reflects effective vascular surface area, rather than the intrinsic permeability of the membrane!)

Twardowski Blood Purif 7: 95-108, 1989

The original 2.27% PET test

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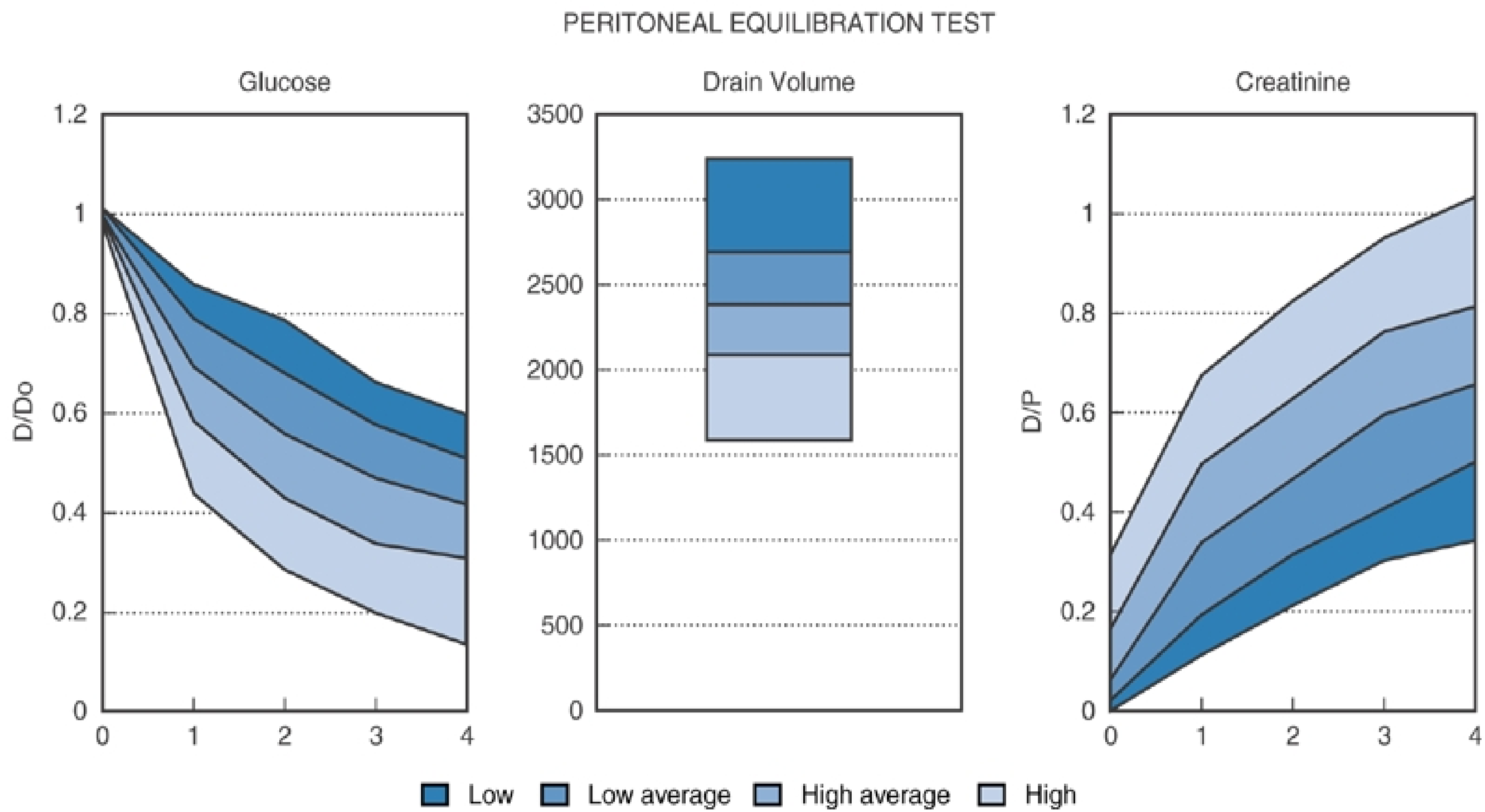

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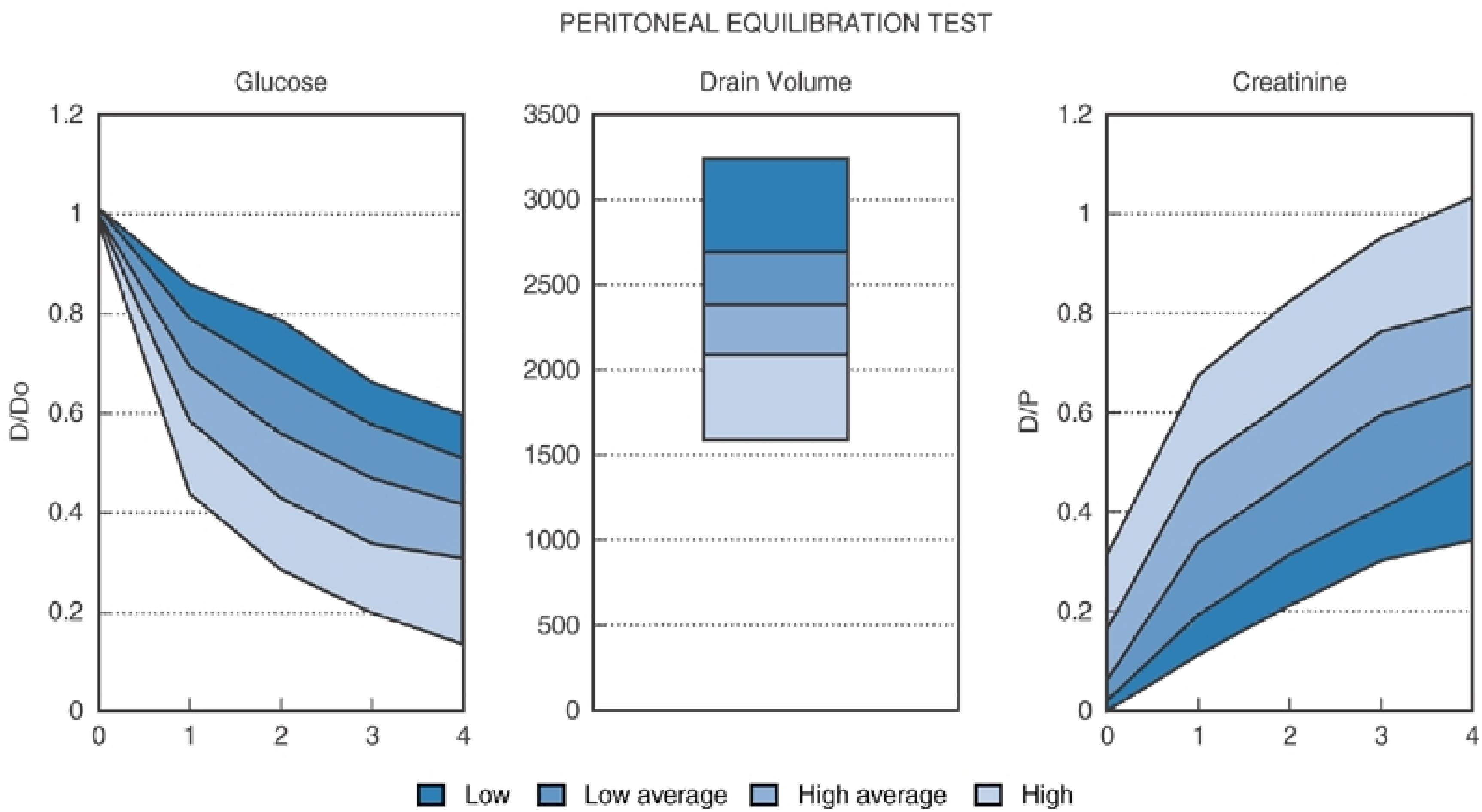
self-care dialysis symposium

ULTRAFILTRATION **SOLUTE TRANSPORT**



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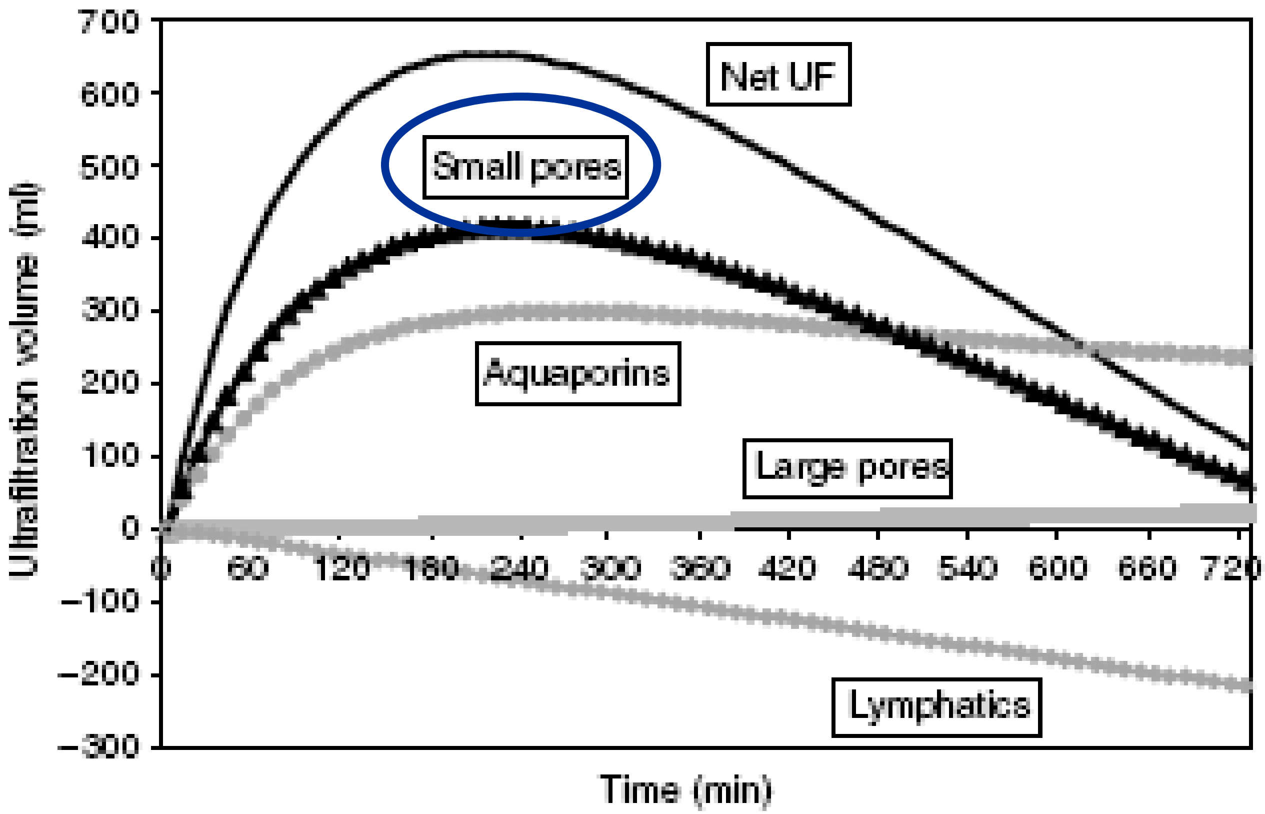

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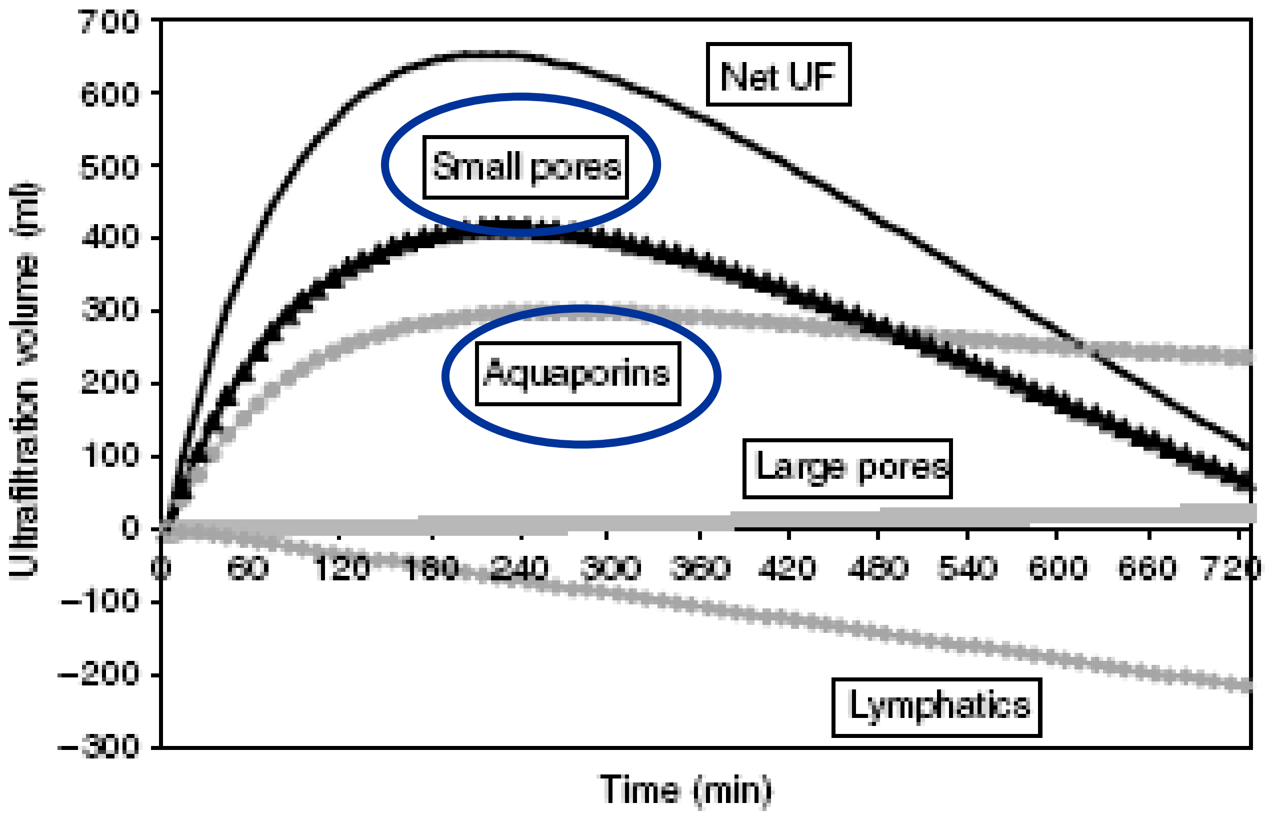
The aquaporins?

ULTRAFILTRATION

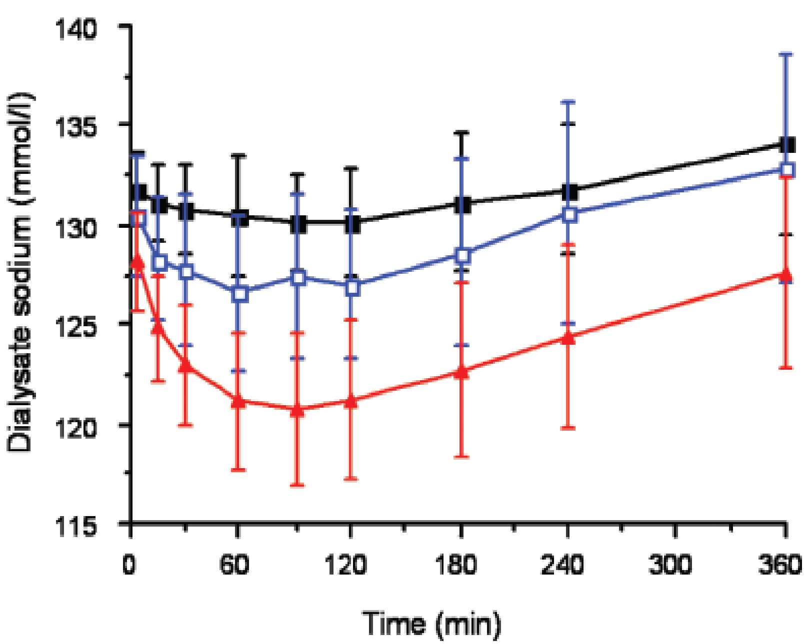


Davies Kidney Int 70 (Suppl 103): 76-83, 2006

Modified (3.86%) PET test

With a hypertonic dialysate solution, dialysate Na^+ concentration will decrease initially due to water-only transport across aquaporins.

= SODIUM SIEVING

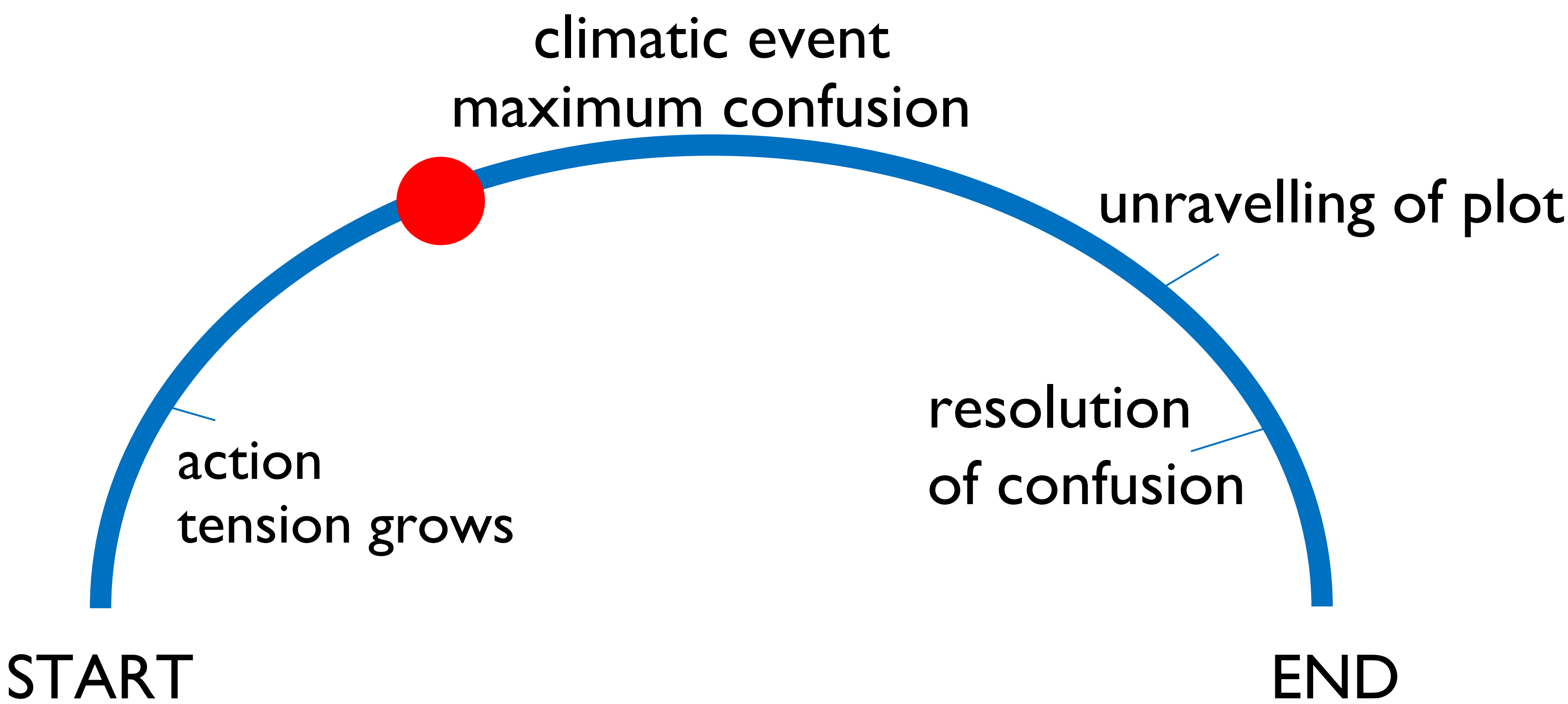


Black: 1.36%; blue: 2.27%; red: 3.86% glucose solution

Time profile D/P$_{sodium}$, D$_{sodium}$ (or D/D0 or ΔD$_{sodium}$ at 1 hour) CAN BE USED TO ASSESS THE CONTRIBUTION OF AQUAPORIN TRANSPORT TO ULTRAFILTRATION

ISPD definition of UF failure = < 400ml UF after 4 hours of 3.86% glucose

Aristotelian Dramatic Arc



Modified (3.86%) PET test

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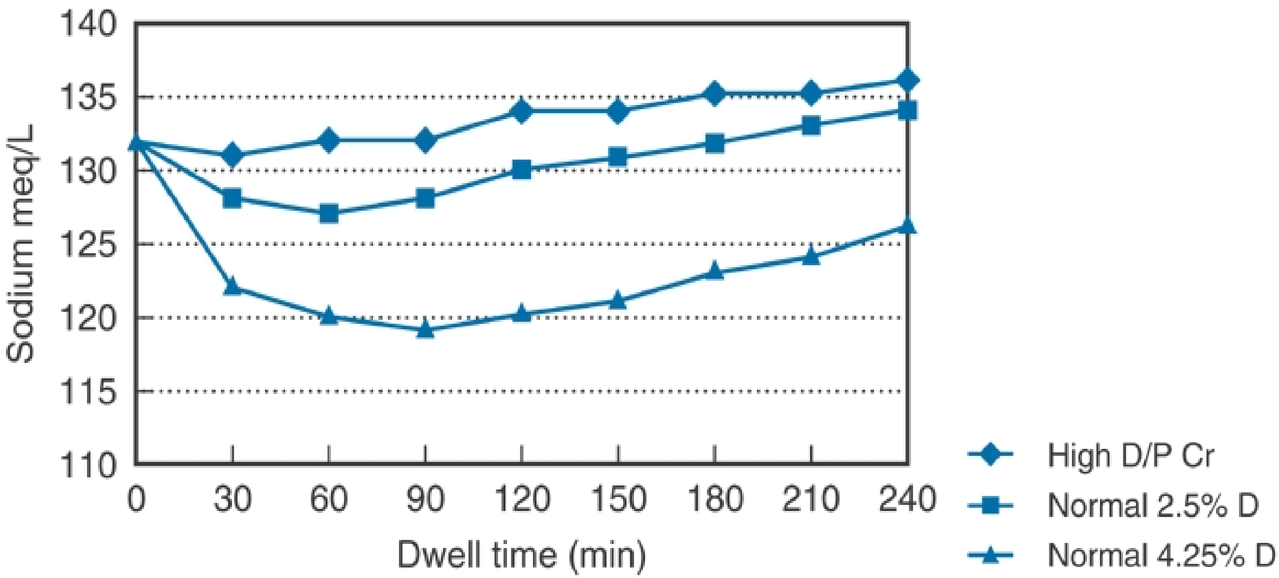
BUT:
A flat SODIUM SIEVING profile may have different meanings!
(at least theoretically)

aquaporin deficiency
“very very fast” small solute transport (small pores)



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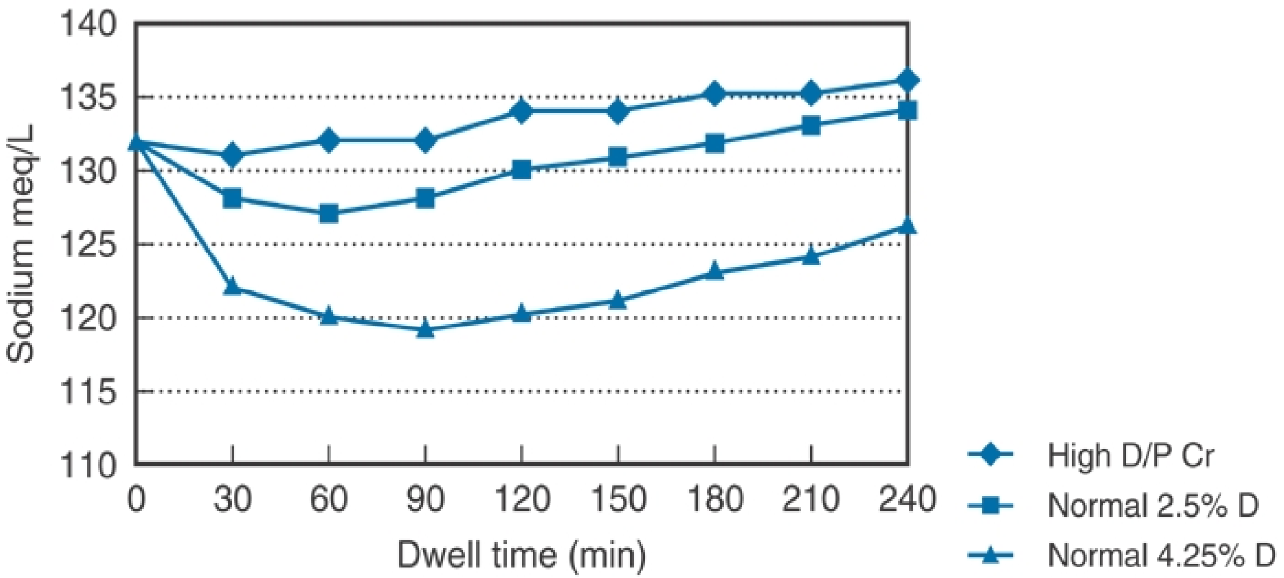

Pore models: interstitium?

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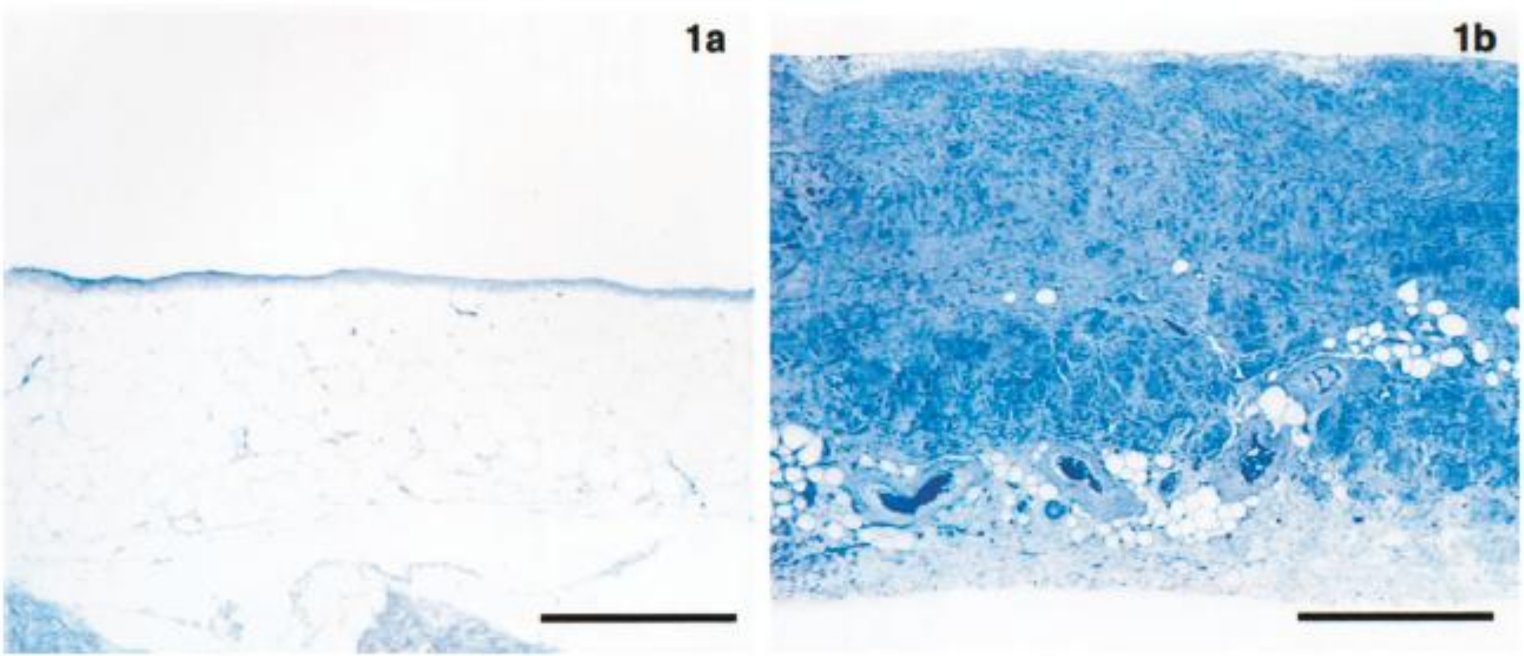
Morphological changes in peritoneal membrane
THICKNESS OF SUBMESOTHELIAL COMPACT ZONE



Normal | After 9 years of PD

Williams et al. J Am Soc Nephrol 13: 470-479, 2002

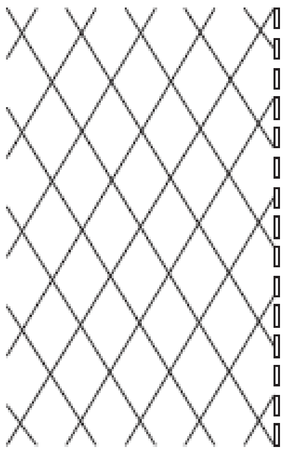
Pore models: interstitium?

the serial three-pore membrane/fiber matrix model

A Three pore membrane with a normal ("loose") serial fiber matrix

ε = 0.995
r_f = 6 (Å)

$L_pS\sigma_g$	= 3.66	µL/min/mmHg
PS_g	= 9.30	mL/min
σ_g	= 0.047	
L_pS	= 0.078	mL/min/mmHg

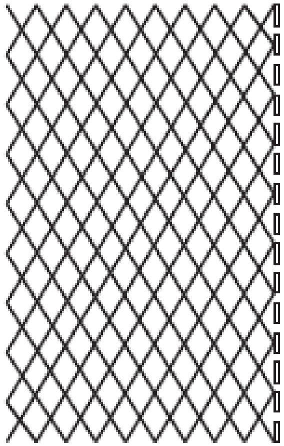


S = 1

B Three pore membrane with a fibrotic ("dense") serial fiber matrix

ε = 0.96
r_f = 7.5 (Å)

$L_pS\sigma_g$	= 3.02	µL/min/mmHg
PS_g	= 13.46	mL/min
σ_g	= 0.039	
L_pS	= 0.078	mL/min/mmHg



S = 1.8

Rippe et al. Am J Physiol Renal Physiol 292: F1035-F1043, 2007

Pore models: interstitium?

self-care dialysis
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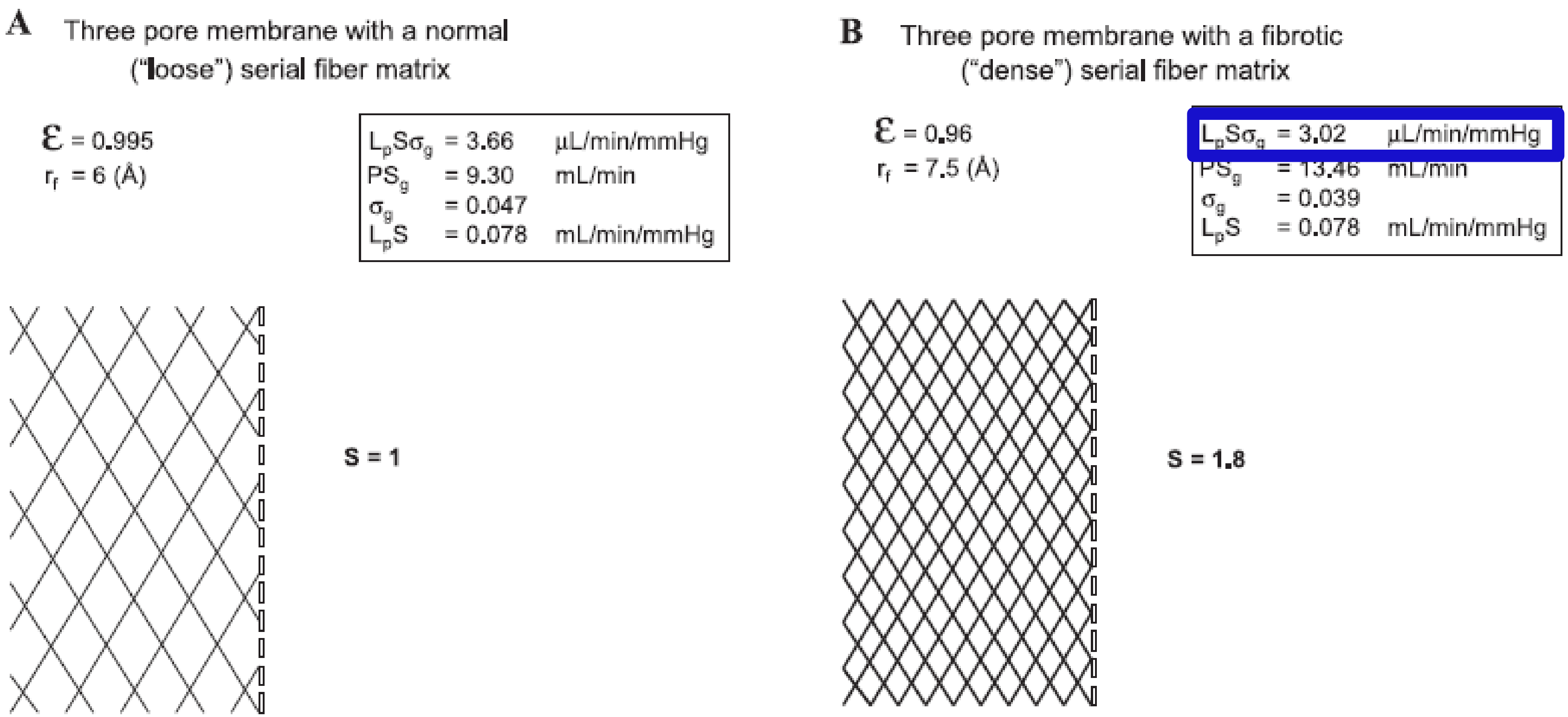
the serial three-pore membrane/fiber matrix model



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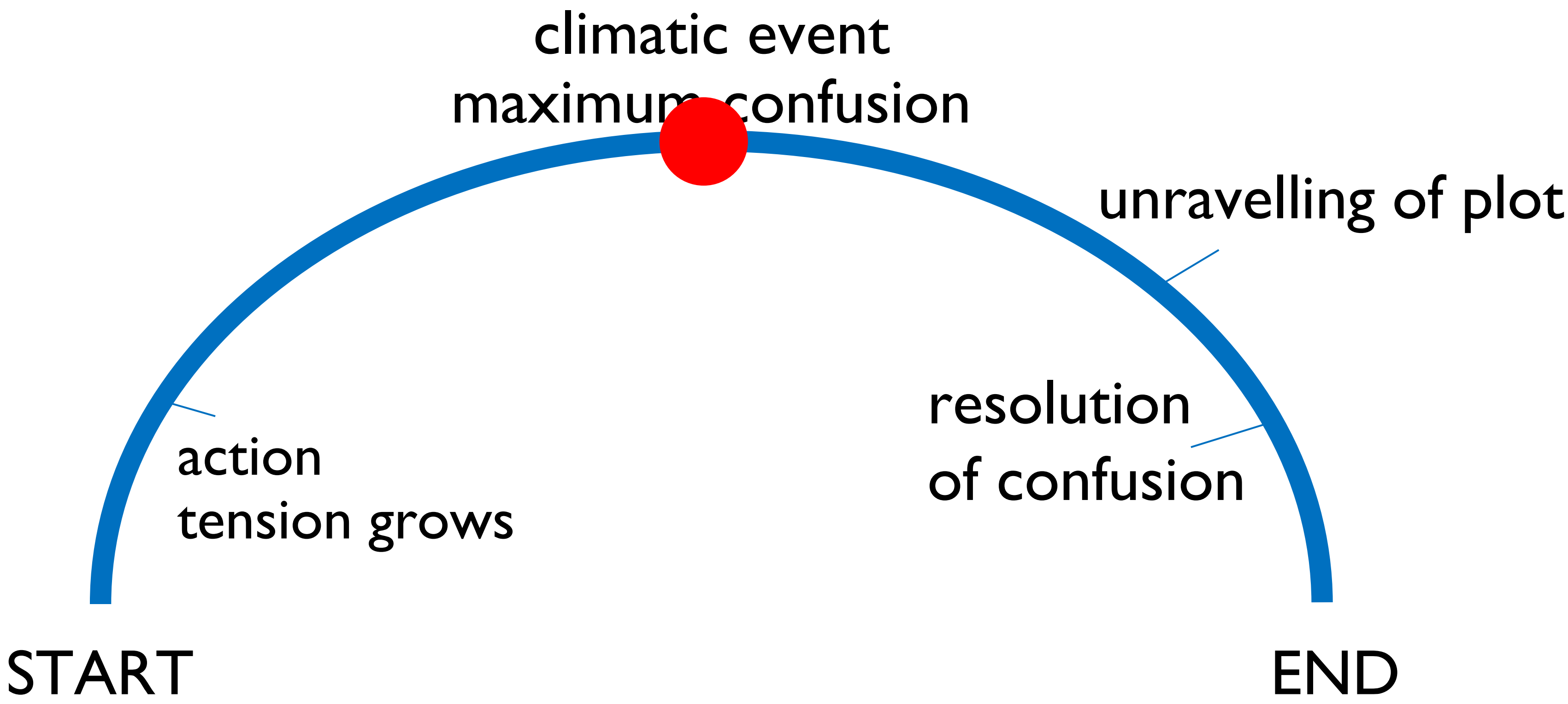

Please welcome: OCG!

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The Osmotic Conductance to Glucose

= the ability of glucose to exert an osmotic pressure sufficient to cause transperitoneal ultrafiltration

= $L_p.S.\sigma$ (µl/min/mmHg)

B Three pore membrane with a fibrotic ("dense") serial fiber matrix

ε = 0.96
r_f = 7.5 (Å)

$L_pS\sigma_g$	= 3.02	µL/min/mmHg
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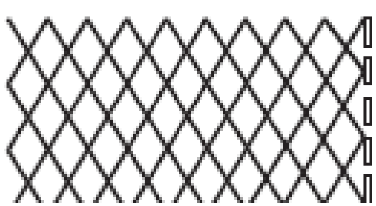


Rippe et al. Am J Physiol Renal Physiol 292: F1035-F1043, 2007

OCG: the Dummy's view

$L_p.S.\sigma$ (µl/min/mmHg)

Reflection coefficient of glucose

= lower in case of aquaporin dysfunction

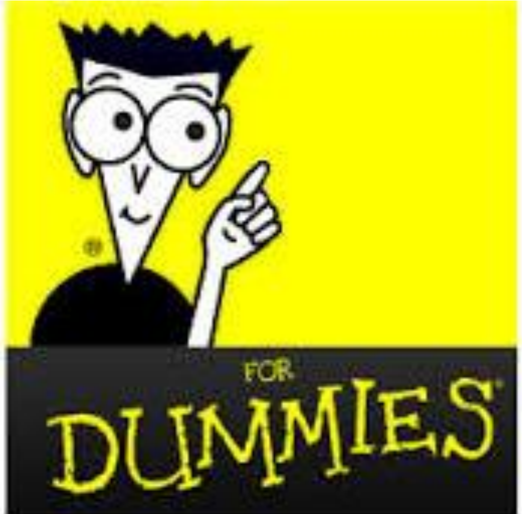
= lower in case of increased small solute transport

Surface area

= higher in case of increased small solute transport

Hydraulic conductivity

= lower in case of fibrosis



OCG: the Dummy's view

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A flat SODIUM SIEVING profile may have different meanings! (at least theoretically)

$L_p.S.\sigma$ (µl/min/mmHg)

aquaporin deficiency

"very very fast" small solute transport (small pores)

fibrotic peritoneal interstitium ("closed membrane", uncoupling)

	OCG	Free water transport	Small pore water transport
Reference	normal	normal	normal
Increased small solute transport	normal	normal	low
Aquaporin dysfunction	low	low	normal
Fibrotic interstitium	low	low	low

OCG: the Dummy's view

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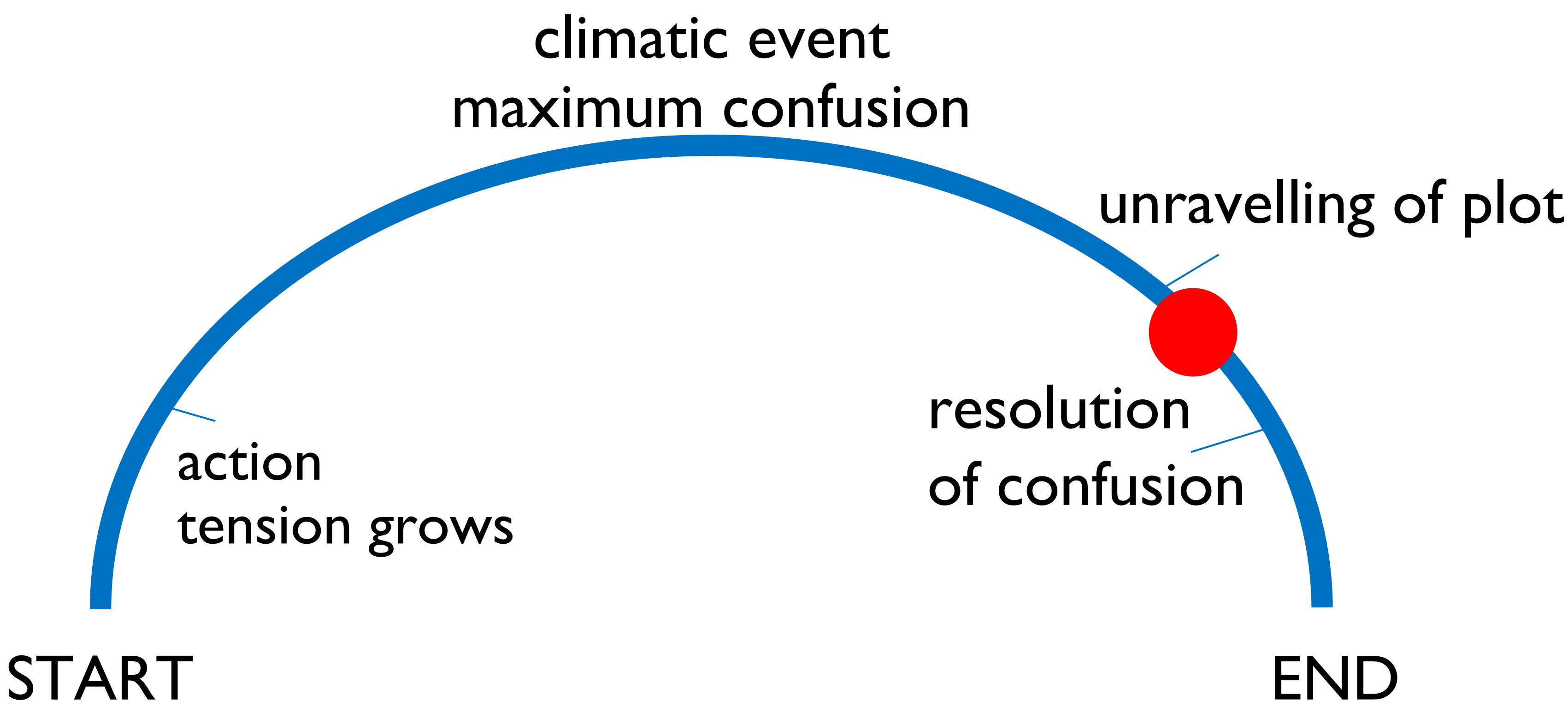
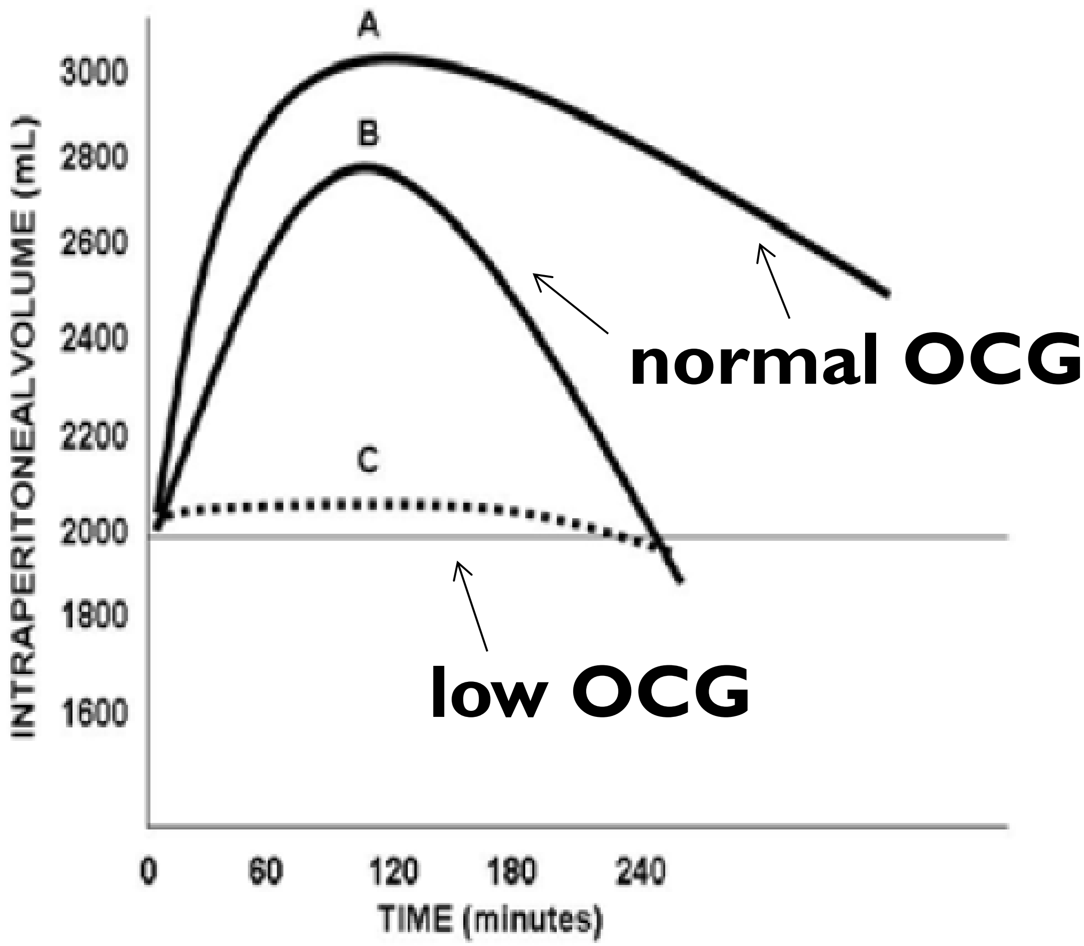
	OCG	Free water transport	Small pore water transport
Reference	normal	normal	normal
Increased small solute transport	normal	normal	low
Aquaporin dysfunction	low	low	normal
Fibrotic interstitium	low	low	low

'isolated aquaporin dysfunction probably non-existent' (Rippe a.o.)

Aristotelian Dramatic Arc

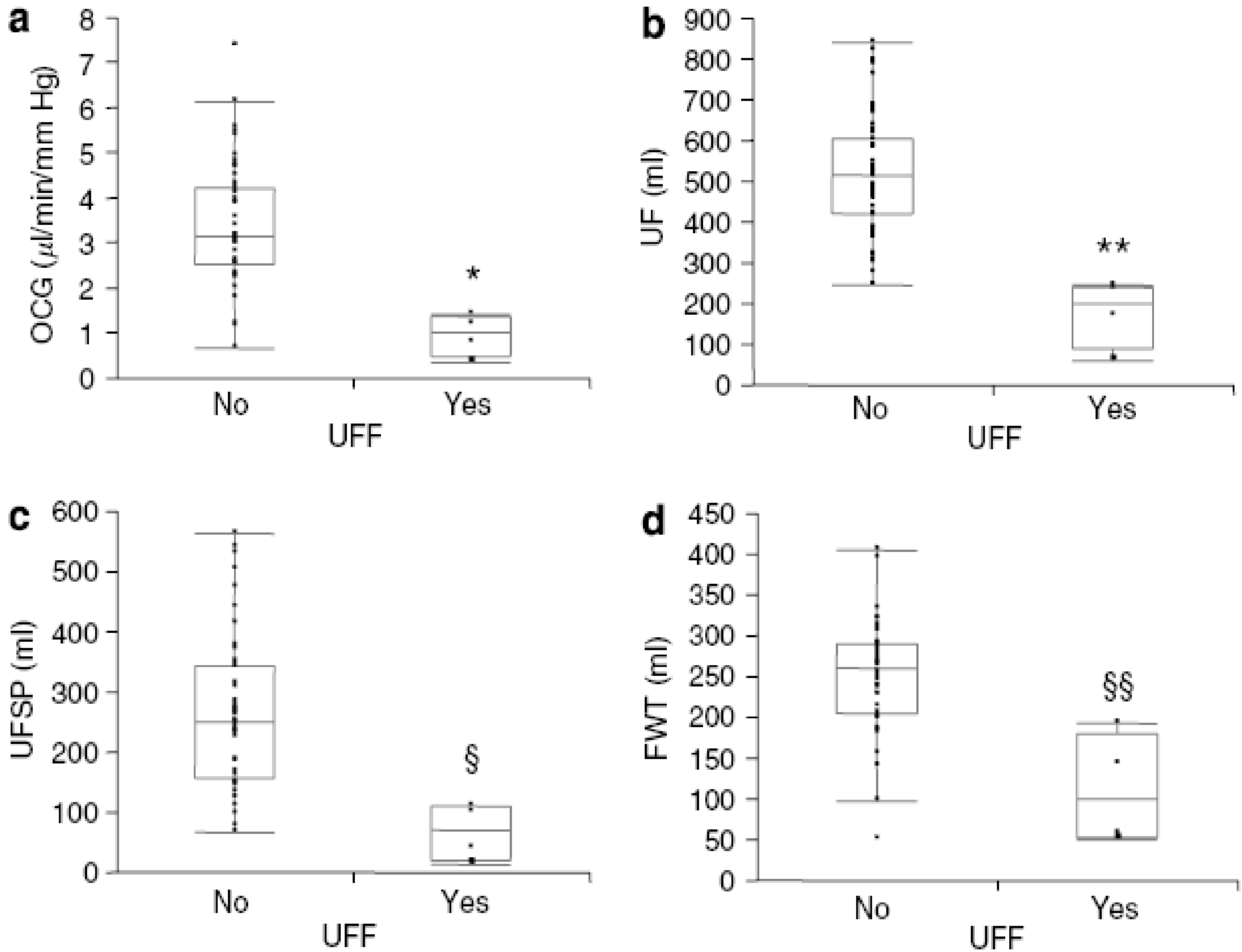


OCG: what does it mean?



La Milia *et al.* J Nephrol 23: 633-647, 2010

OCG: what does it mean?

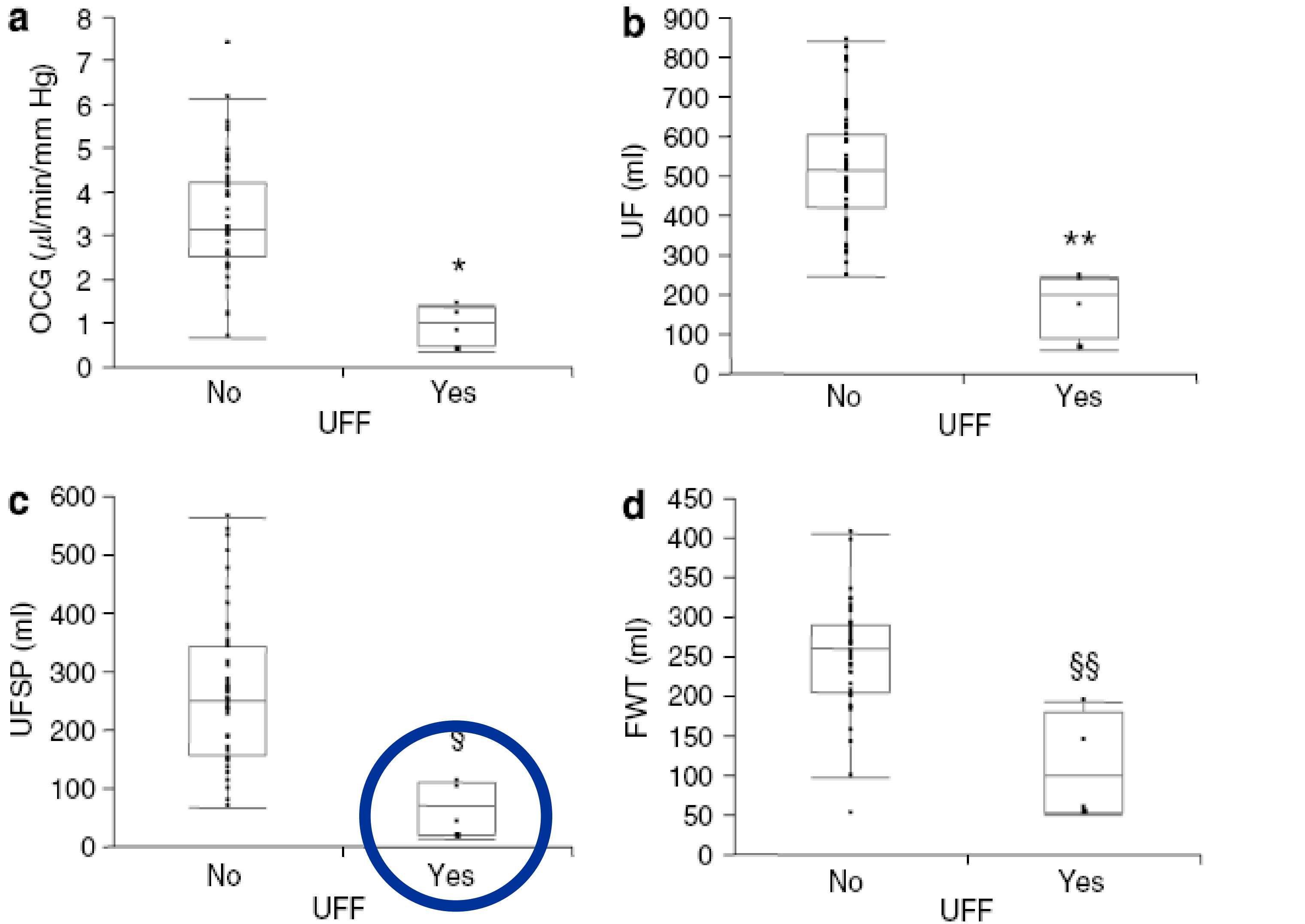


Double mini-PET test

La Milia *et al.* Kidney Int 72: 643-650, 2007

OCG: what does it mean?

self-care dialysis symposium



Double mini-PET test

La Milia *et al.* Kidney Int 72: 643-650, 2007

OCG: what does it mean?

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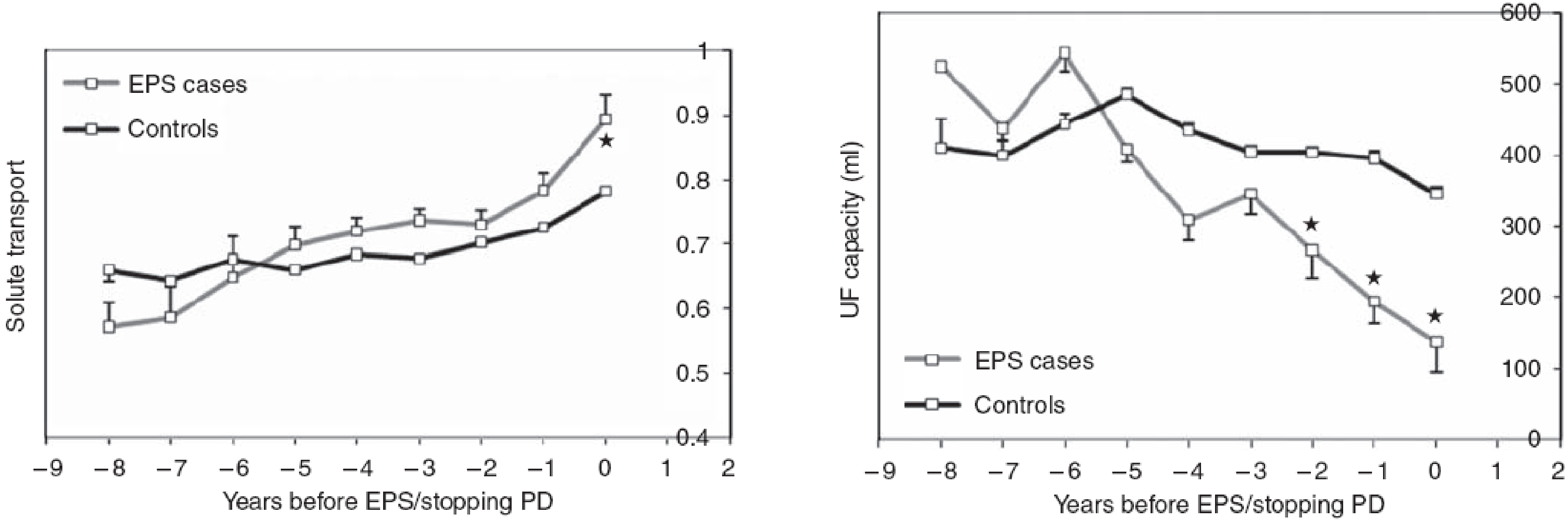
The peritoneal osmotic conductance is low well before the diagnosis of encapsulating peritoneal sclerosis is made

Mark L. Lambie[1,2], Biju John[1,2], Lily Mushahar[1,2], Christopher Huckvale[1,2] and Simon J. Davies[1,2]



Lambie *et al.* Kidney Int 78: 611-618, 2010

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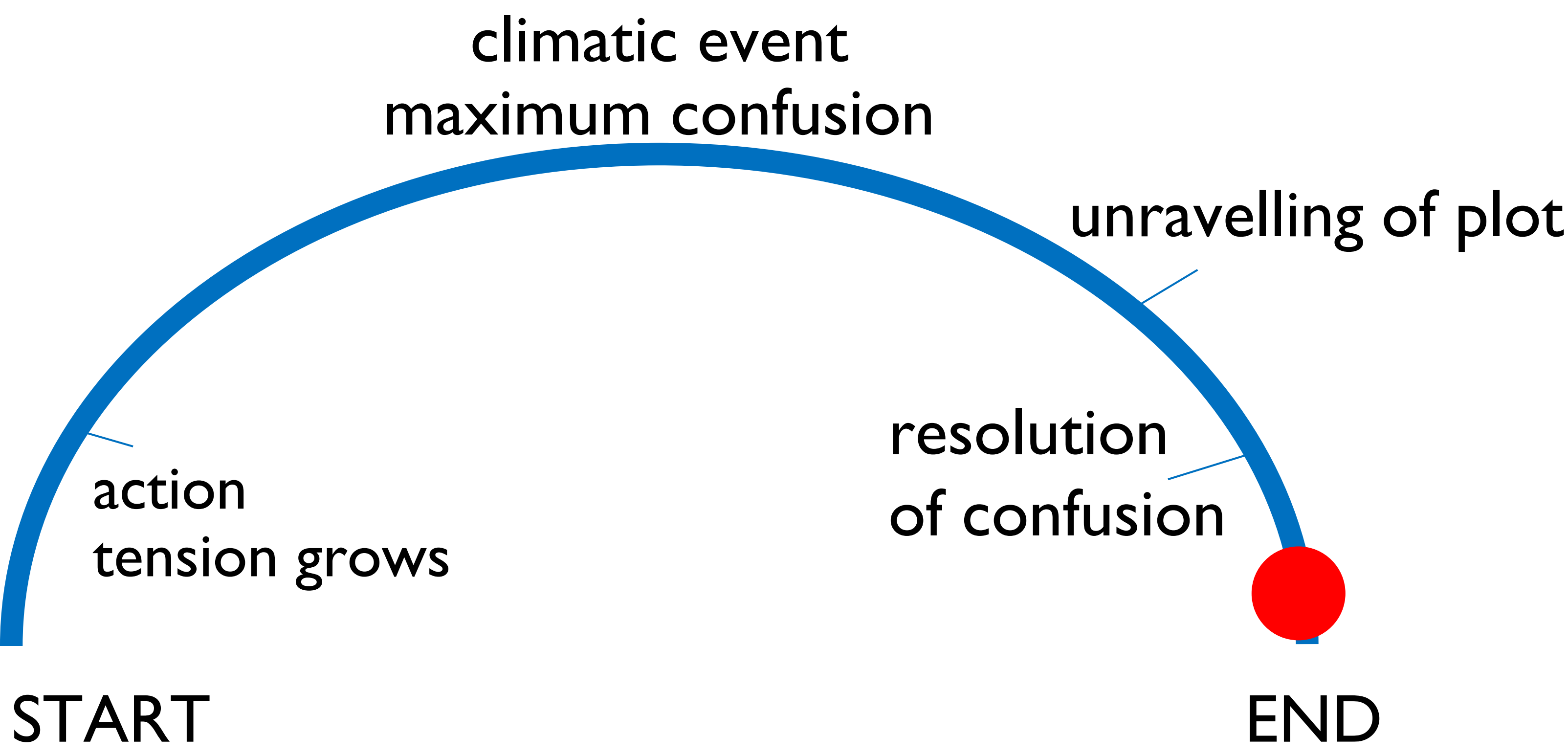
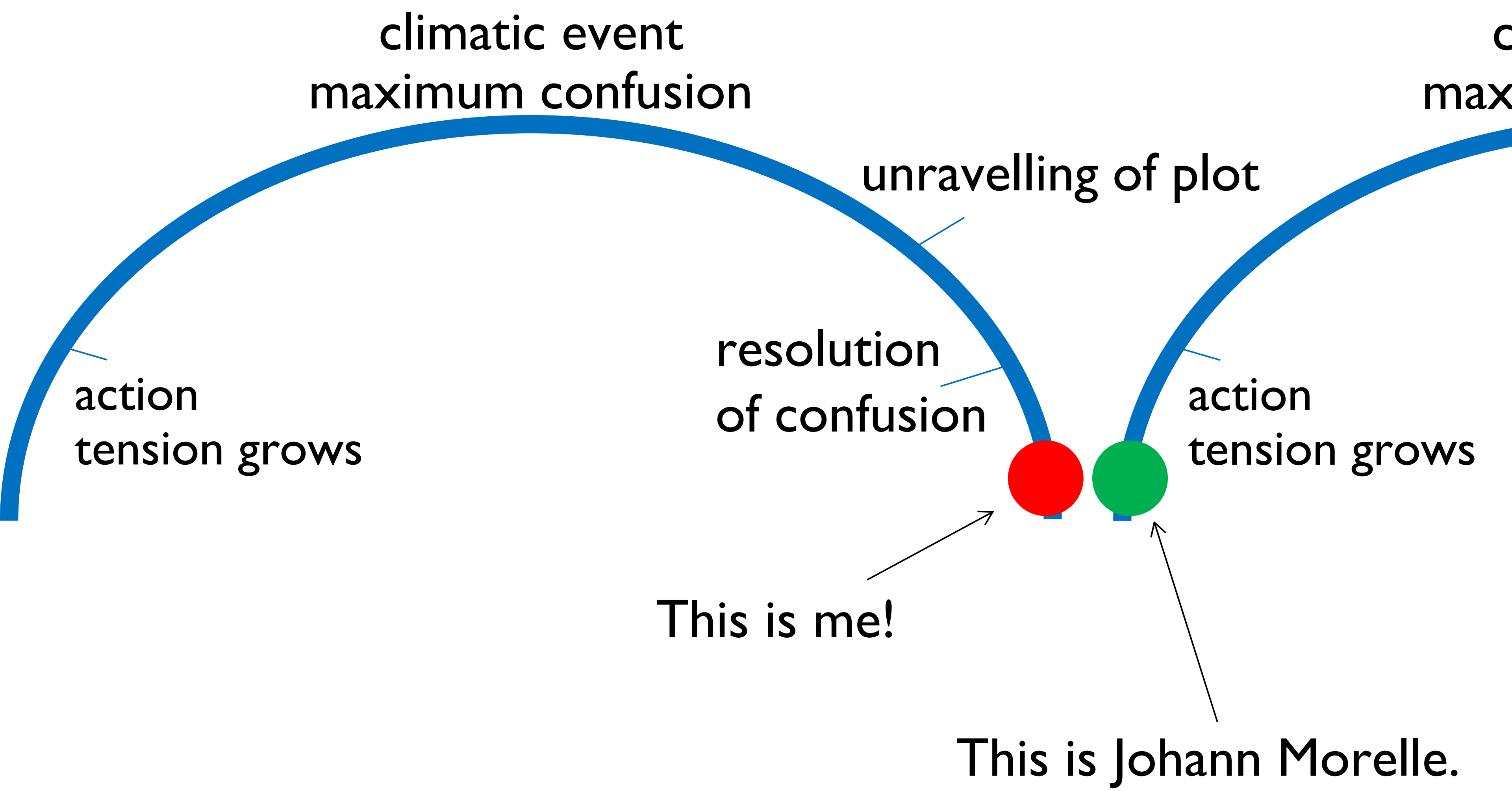


Aristotelian Dramatic Arc

self-care dialysis symposium



Osmotic Conductance to Glucose: What does it mean?

B. Bammens, MD, PhD

Brussels, May 22 2014

UZ LEUVEN BELGIUM

self-care dialysis symposium

2nd self-care dialysis symposium