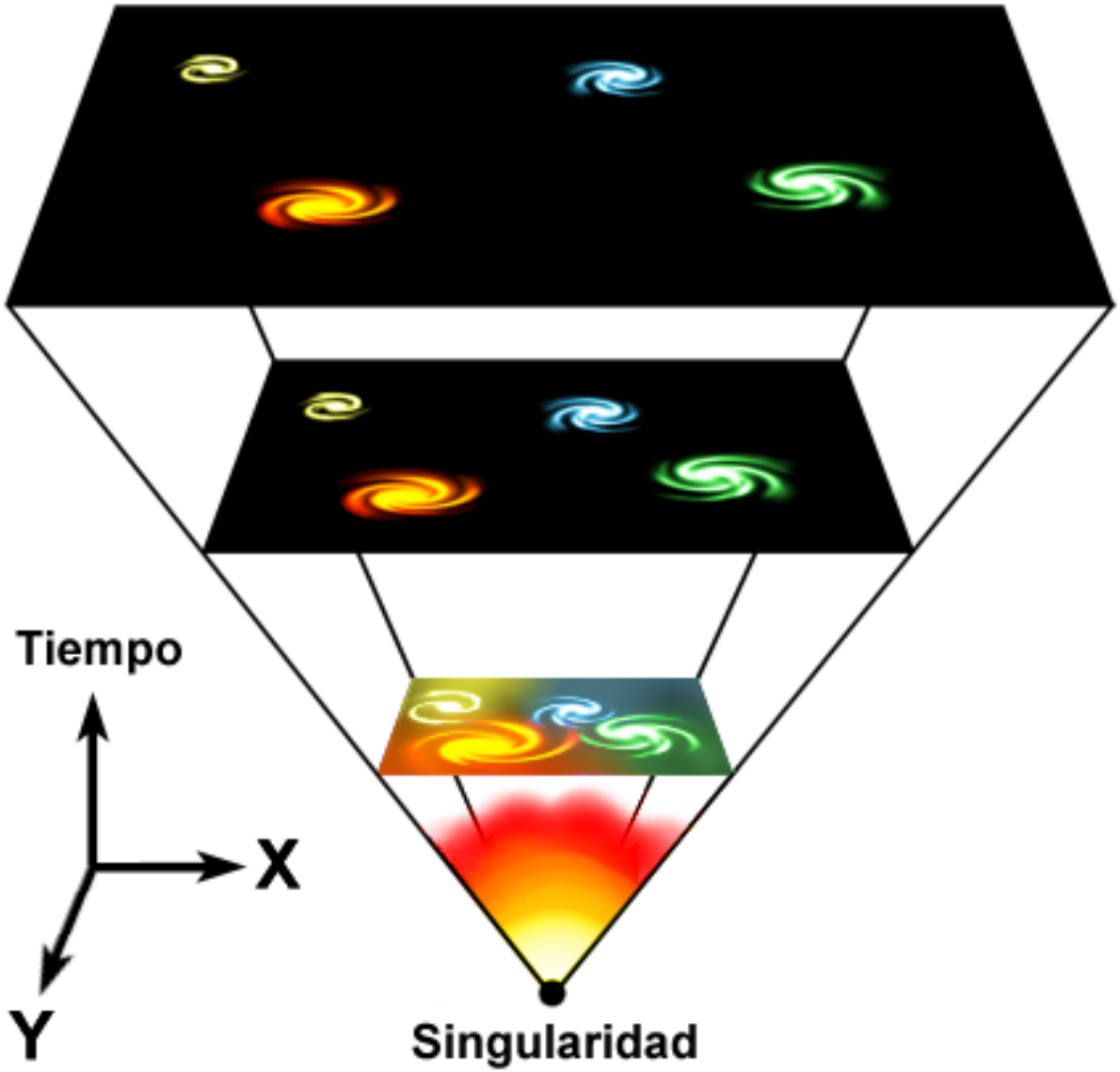
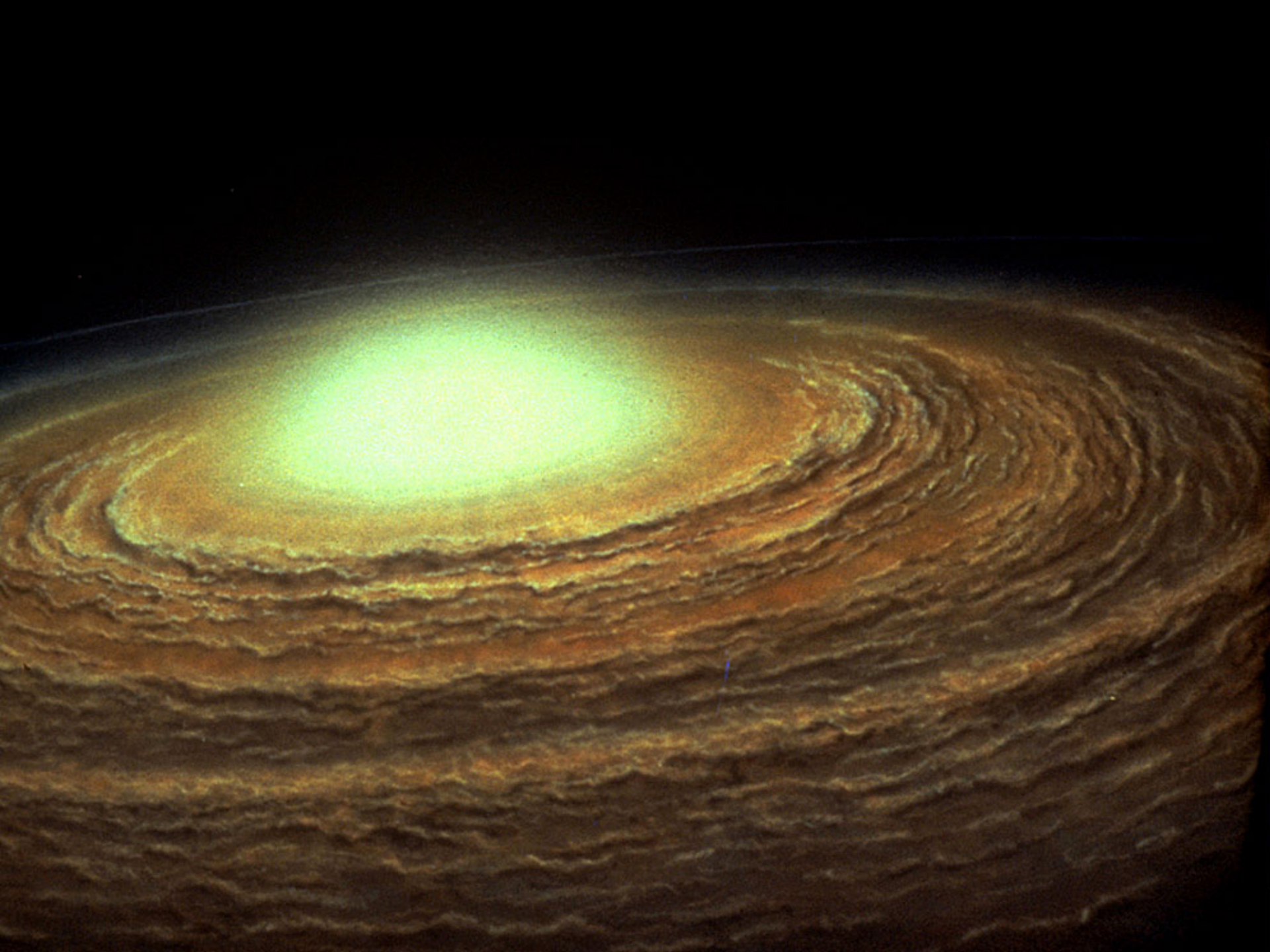
SODIO, PROTEINURIA Y ENFERMEDAD RENAL CRÓNICA

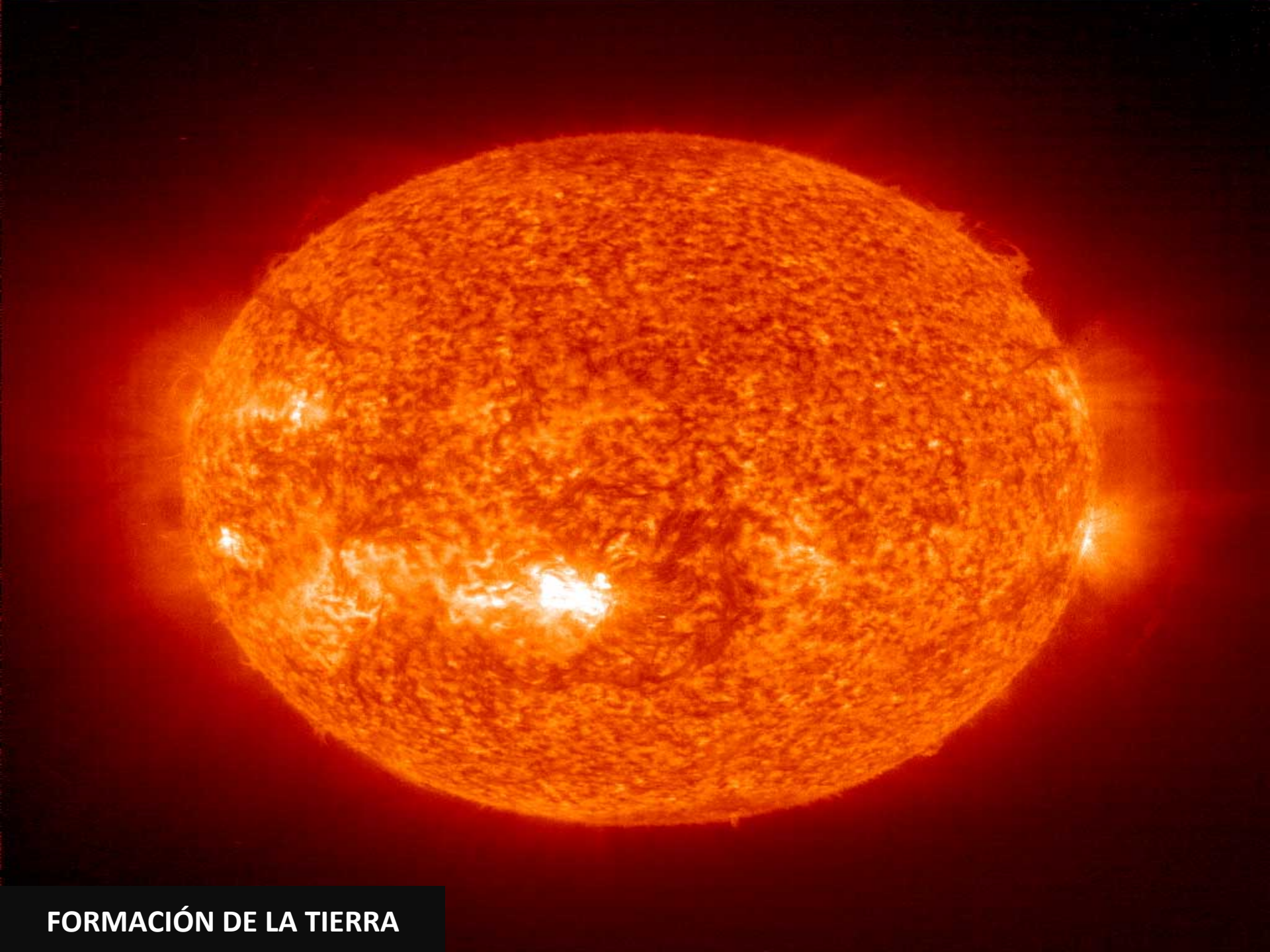
HERNÁN TRIMARCHI

HOSPITAL BRITÁNICO DE BUENOS AIRES

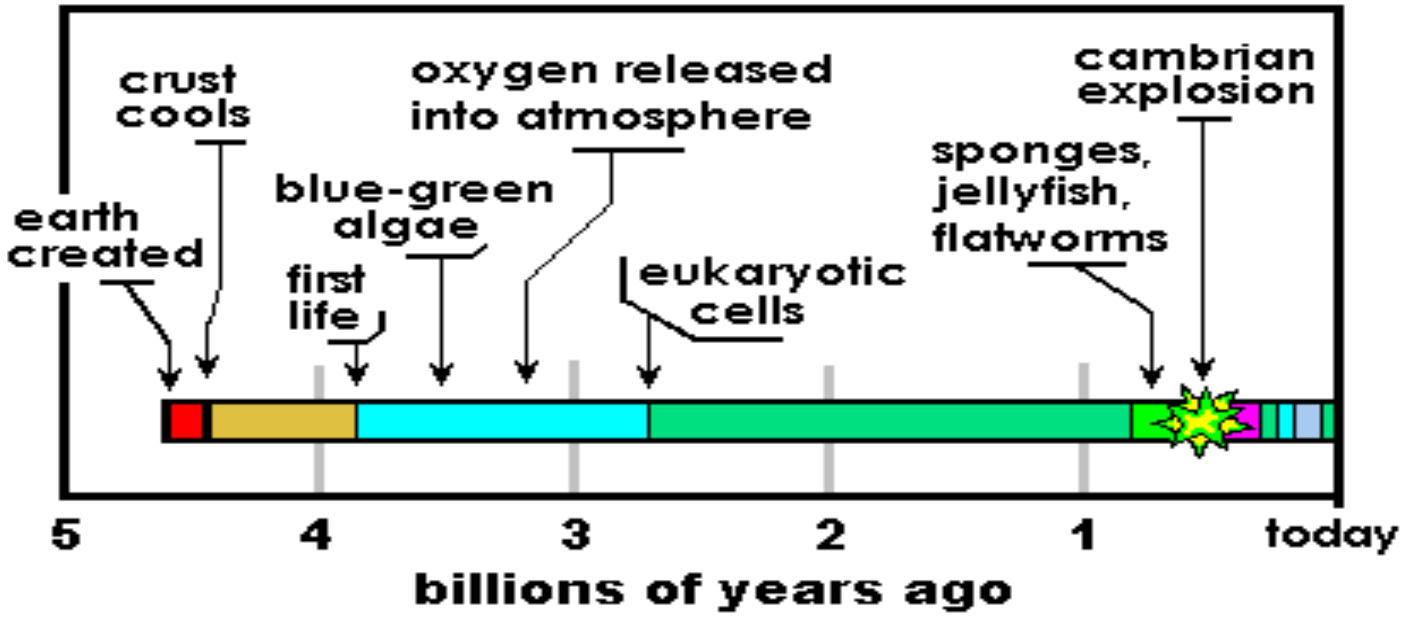
SERVICIO DE NEFROLOGÍA


Tiempo
X
Y
Singularidad

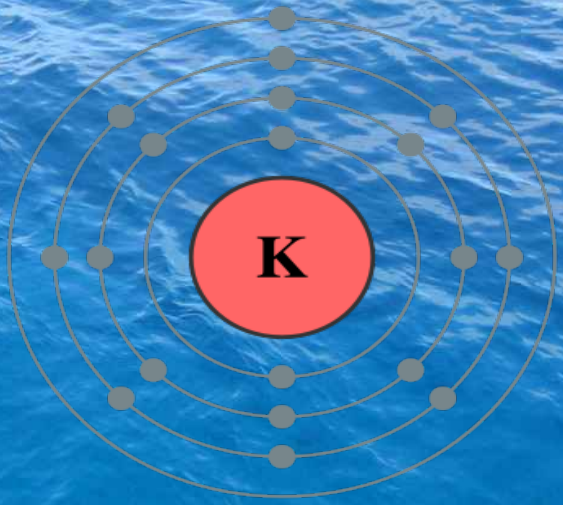


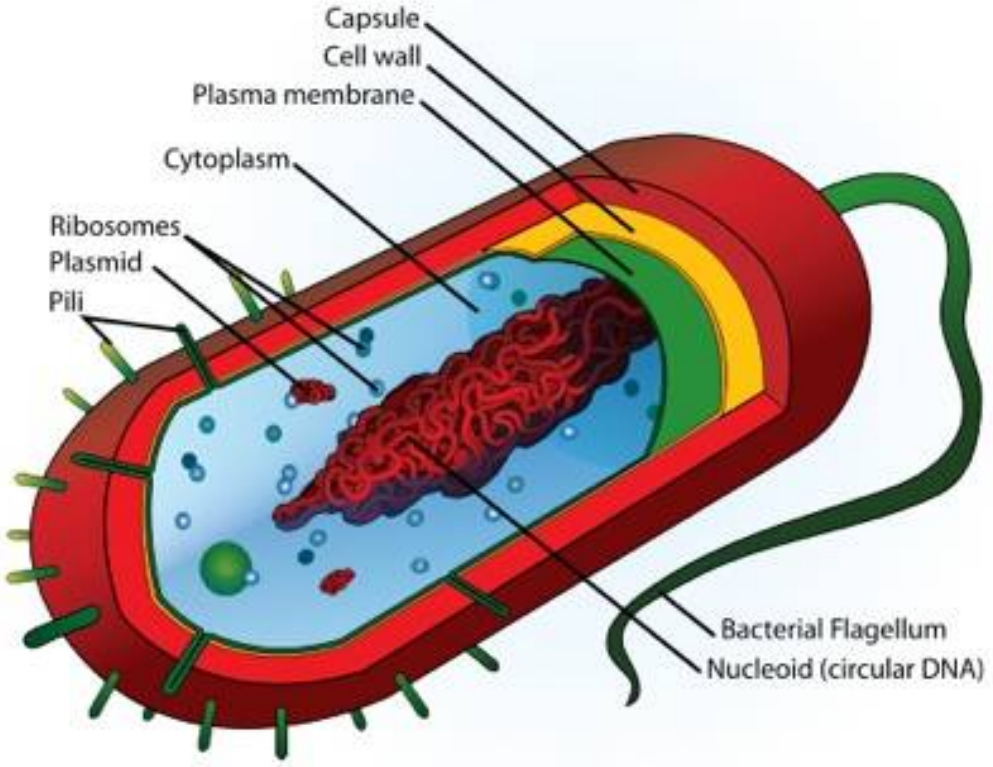


FORMACIÓN DE LA TIERRA

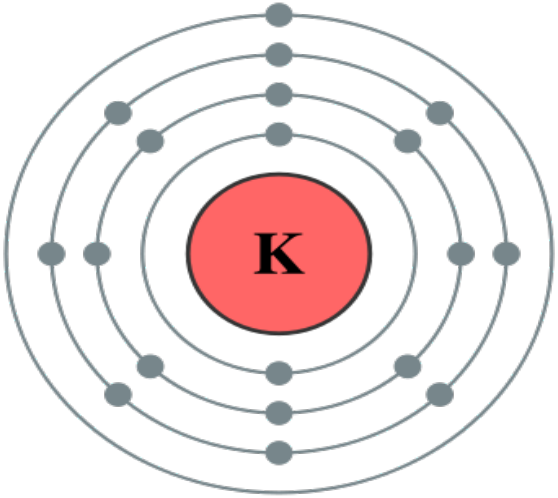

crust cools
oxygen released into atmosphere
cambrian explosion
sponges, jellyfish, flatworms
blue-green algae
earth created
first life
eukaryotic cells
5
4
3
2
1
today
billions of years ago

19: Potassium **2,8,8,1**

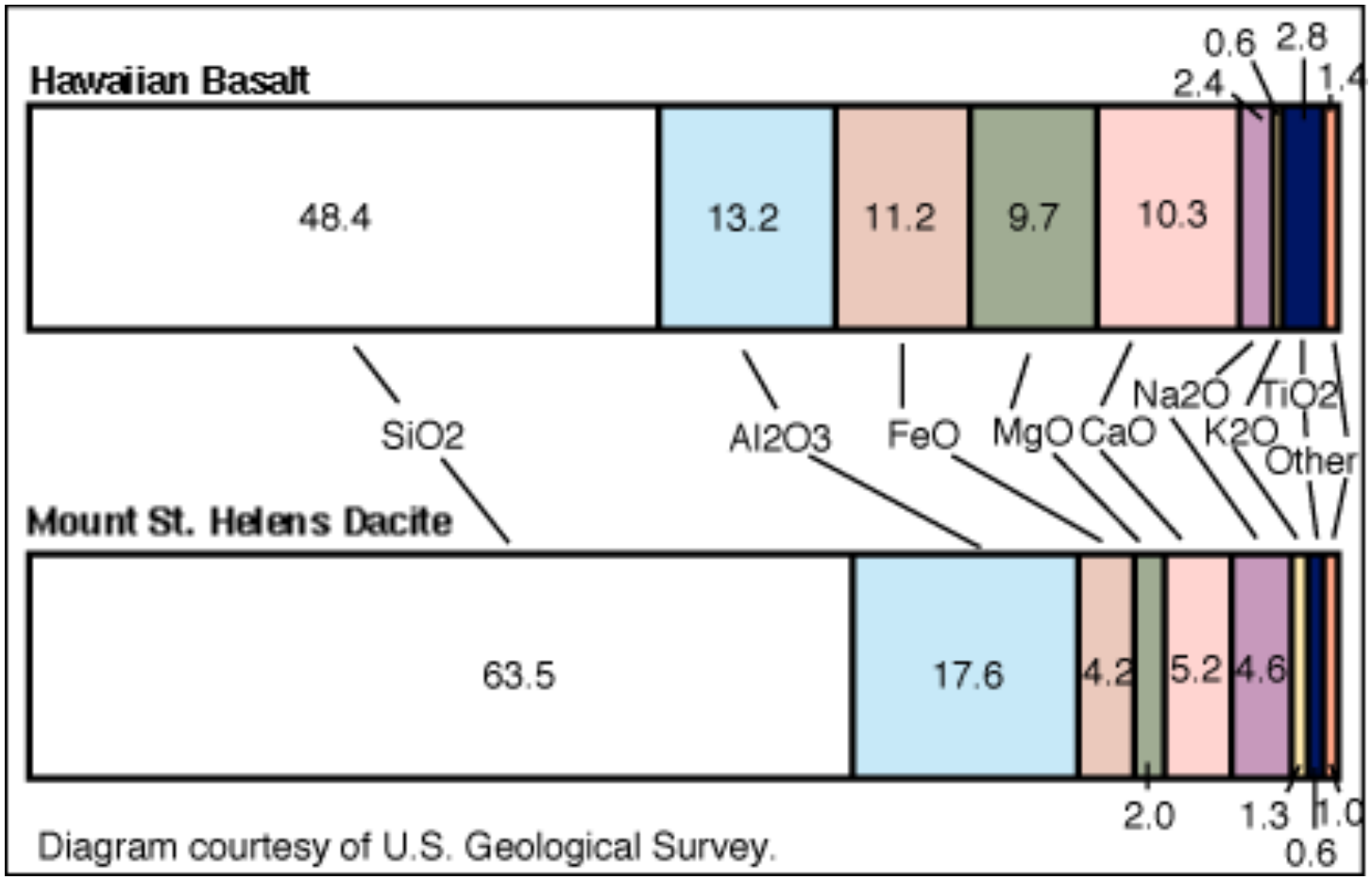




19: Potassium **2,8,8,1**

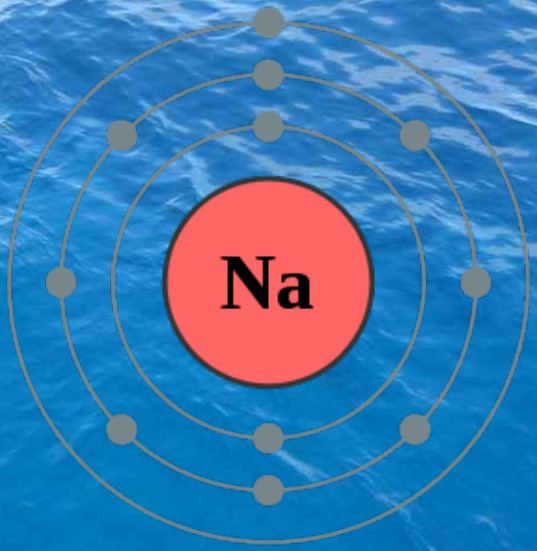


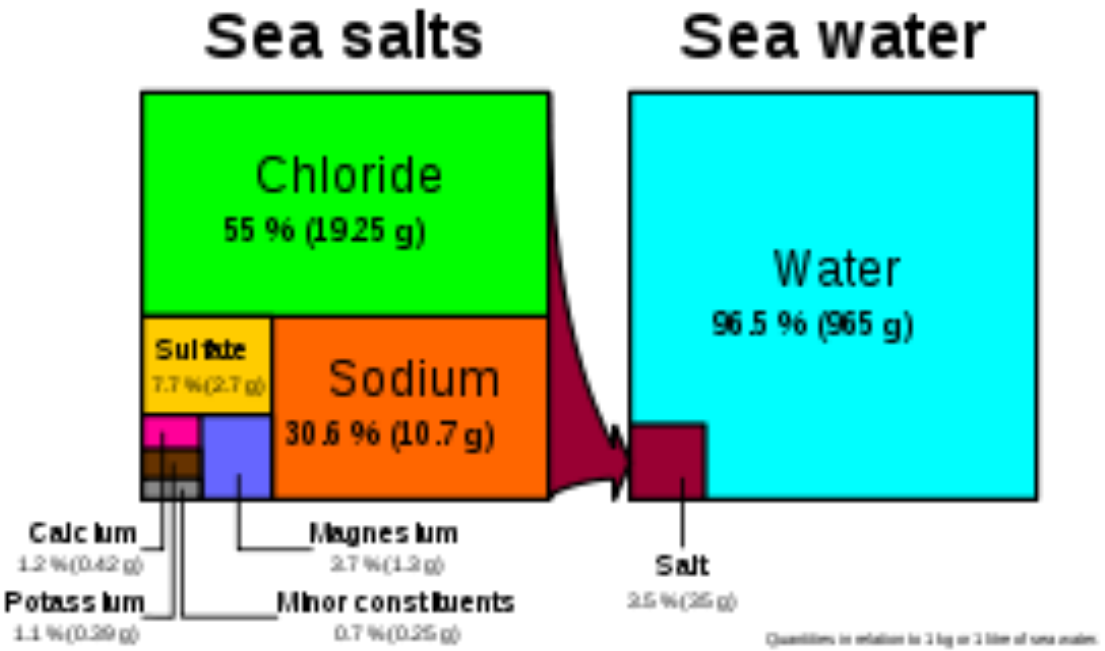
sodio


Hawaiian Basalt
48.4
13.2
11.2
9.7
10.3
2.4
0.6
2.8
1.4
SiO2
Al2O3
FeO
MgO
CaO
Na2O
K2O
TiO2
Other
Mount St. Helens Dacite
63.5
17.6
4.2
5.2
4.6
2.0
1.3
1.0
0.6
Diagram courtesy of U.S. Geological Survey.

sodio

11: Sodium 2,8,1

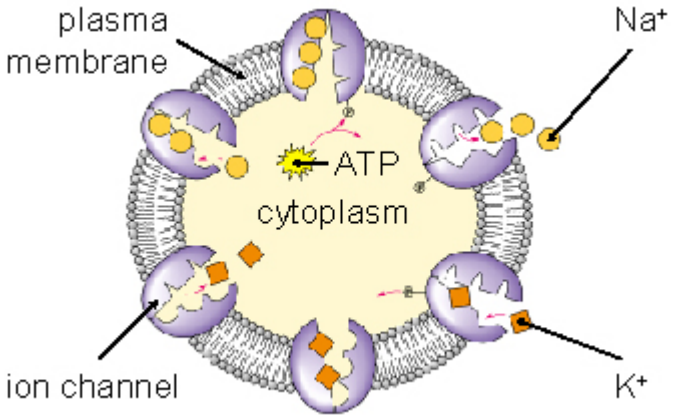


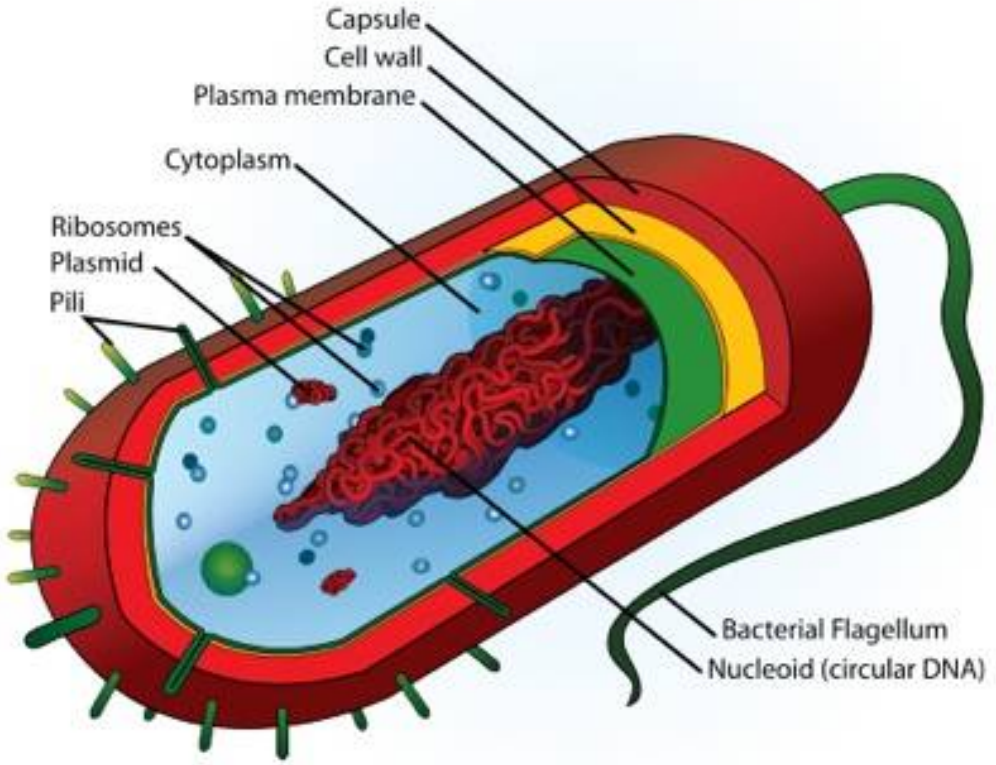


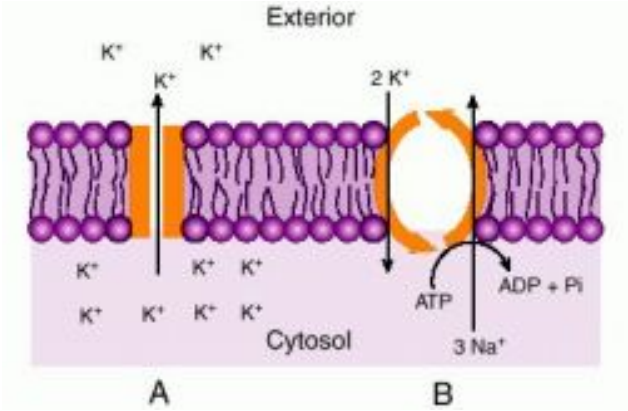
Comparison of Major Elements in the Dead Sea, the Mediterranean sea and Typical ocean Water.			
	Dead Sea	Mediterranean Sea	Ocean Water
Chloride	224,900	22,900	19,000
Magnesium	44,000	1,490	1,350
Sodium	40,100	12,700	10,500
Calcium	17,200	470	400
Potassium	7,650	470	390
Bromide	5,300	76	65

sodio

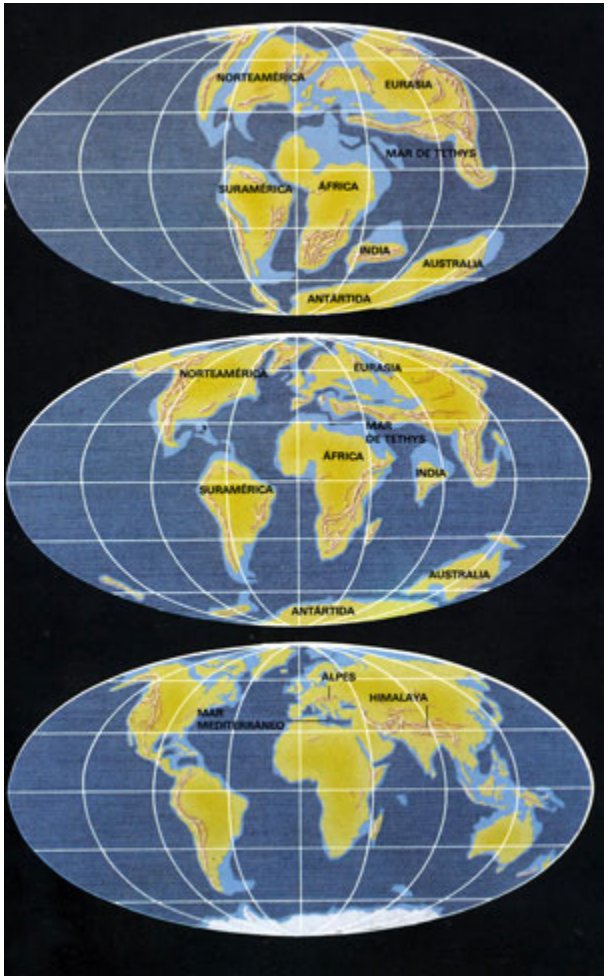
sodio

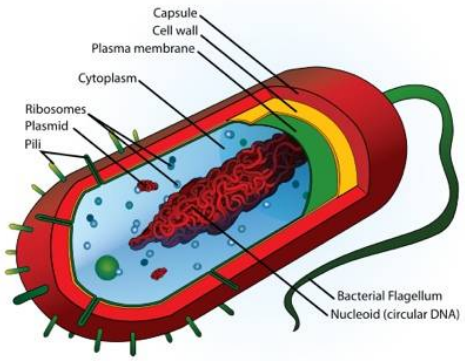

plasma membrane
Na+
ATP
cytoplasm
ion channel
K+


Capsule
Cell wall
Plasma membrane
Cytoplasm
Ribosomes
Plasmid
Pili
Bacterial Flagellum
Nucleoid (circular DNA)

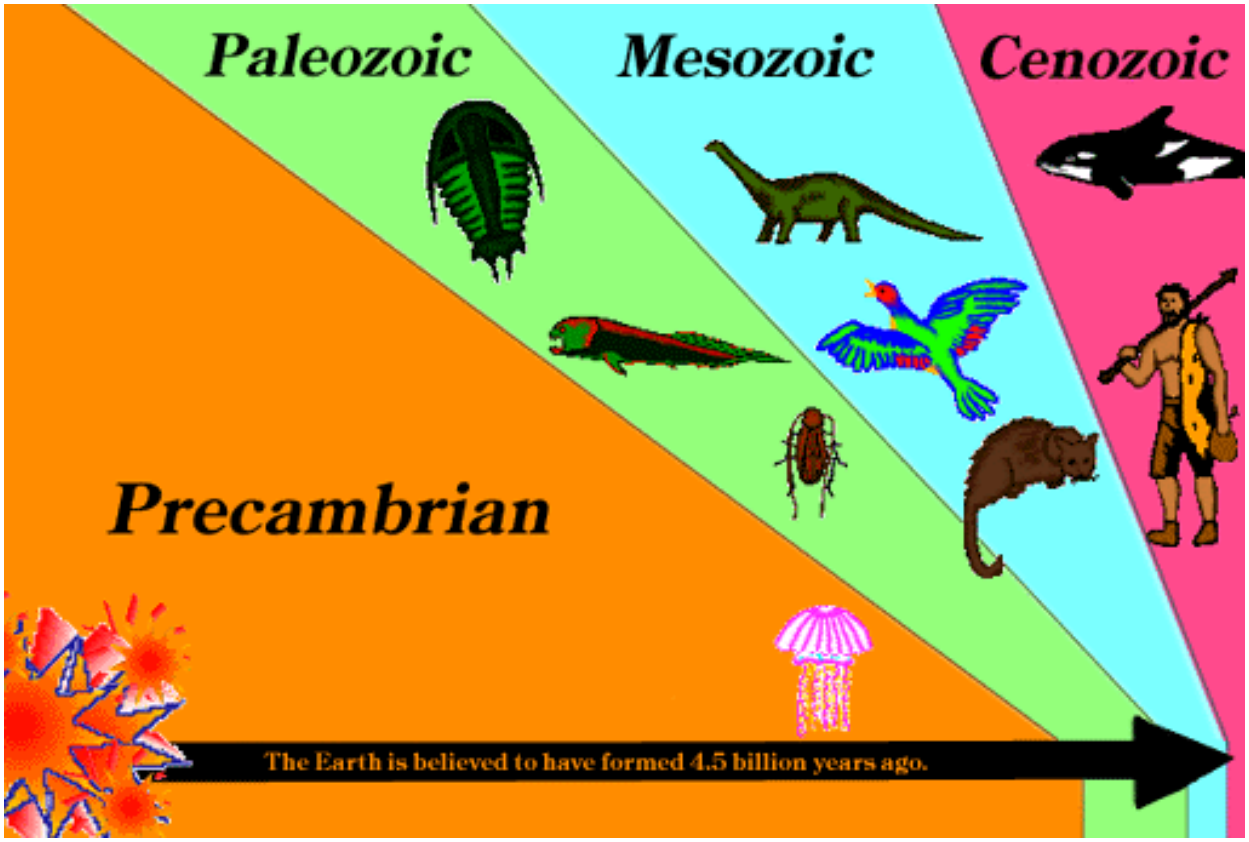

Exterior
K+
2 K+
ATP
ADP + Pi
3 Na+
Cytosol
A
B


Eurasia
North America
Africa
South America
India
Antaretica
Australia


NORTEAMÉRICA
EURASIA
MAR DE TETHYS
SURAMÉRICA
ÁFRICA
INDIA
AUSTRALIA
ANTÁRTIDA
NORTEAMÉRICA
EURASIA
MAR DE TETHYS
ÁFRICA
INDIA
SURAMÉRICA
AUSTRALIA
ANTÁRTIDA
ALPES
HIMALAYA
MAR MEDITERRÁNEO


Capsule
Cell wall
Plasma membrane
Cytoplasm
Ribosomes
Plasmid
Pili
Bacterial Flagellum
Nucleoid (circular DNA)


NATIONAL GEOGRAPHIC
Find more wallpapers at www.nationalgeographic.com
Photograph by Brian J. Skerry


Paleozoic
Mesozoic
Cenozoic
Precambrian
The Earth is believed to have formed 4.5 billion years ago.

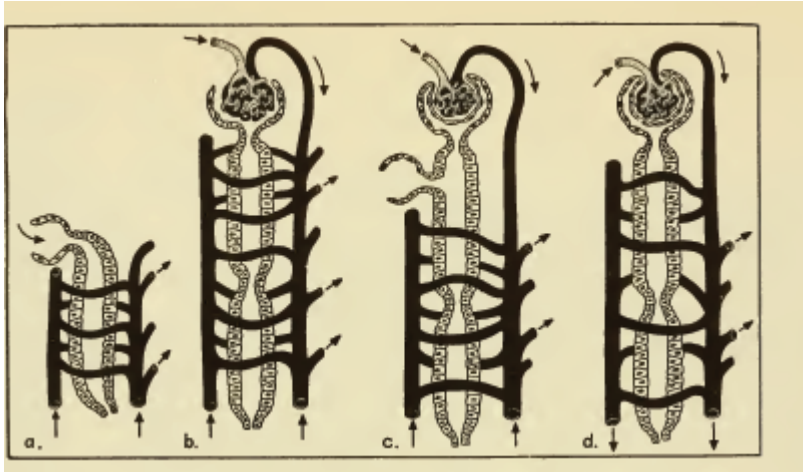
The Natural History Library

$1.45
N10

From Fish to Philosopher

HOMER W. SMITH

A Doubleday Anchor Book
The American Museum of Natural History



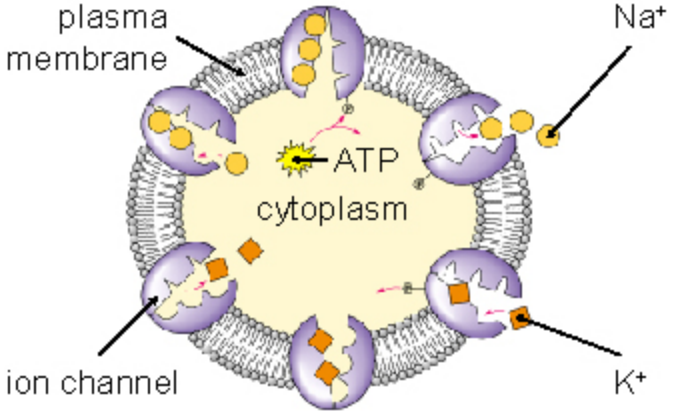
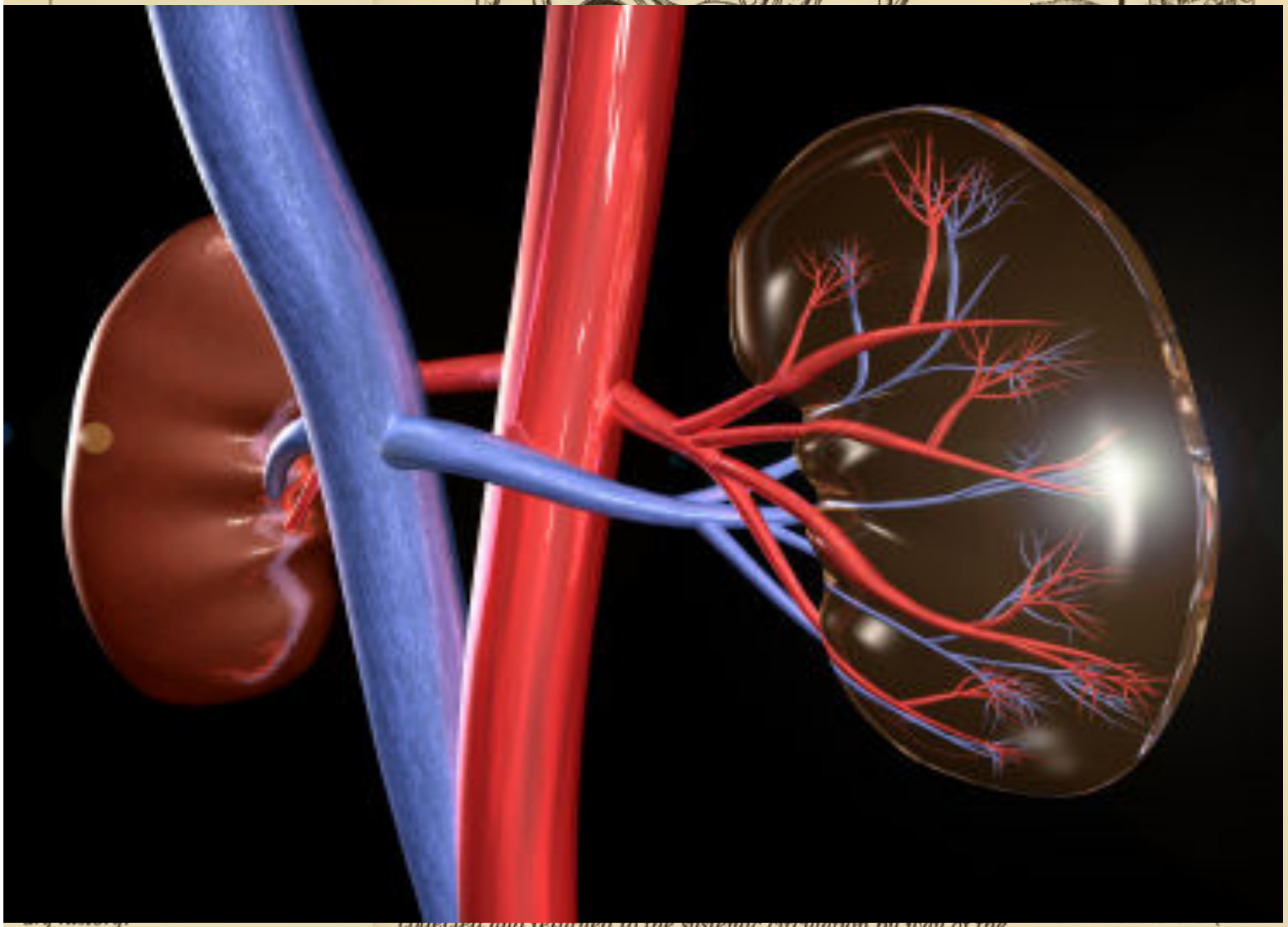


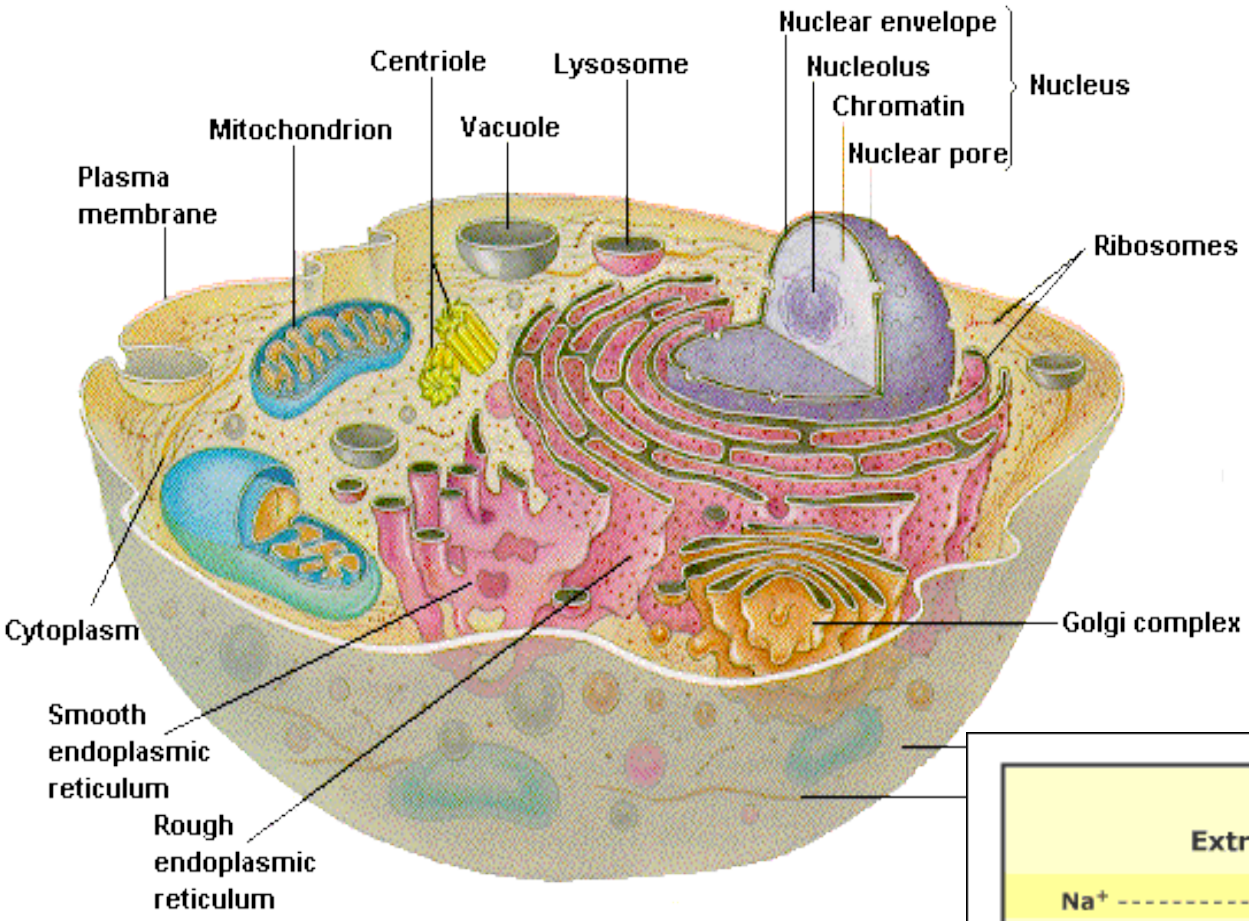
FIGURE 5. Four Stages in the Evolution of the Vertebrate Nephron–*(a) In the protovertebrate the renal tubule drained the coelom or body cavity by means of an open mouth or coelomostome. (b) The glomerulus was evolved in the earliest vertebrates as a device to excrete water, and was at first only loosely related to the coelomostome. (c) Later the glomerulus became sealed within the end of the tubule, the coelomostome persisting in some species. (d) In the higher vertebrates, the coelomostome has disappeared entirely, leaving the typical vertebrate nephron. The primitive blood supply to the protovertebrate tubule persists as the "renal-portal system" in the fishes, Amphibia, reptiles and birds (a to c), but disappears in the mammals (d), leaving the tubules supplied only by post-glomerular blood.*



The time scale is such that the P
years in length) and Recent Time (a

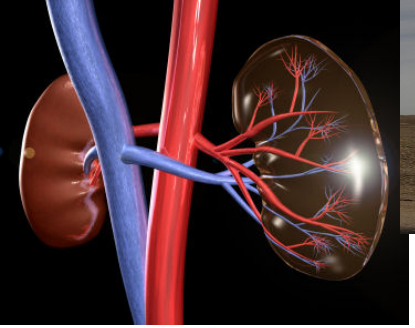
collected and returned to the systemic circulation by way of the renal vein. Each human kidney contains nearly one million such nephrons, all of which are similar in structure and function.

first begin to appear in



sodio

	Extracellular Fluid	Intracellular Fluid
Na^+	142 mEq/L	10 mEq/L
K^+	4 mEq/L	140 mEq/L
Ca^{++}	5 mEq/L	<1 mEq/L
Mg^{++}	3 mEq/L	58 mEq/L
Cl^-	103 mEq/L	4 mEq/L
HCO_3^+	28 mEq/L	10 mEq/L
Phosphates	4 mEq/L	75 mEq/L
SO_4^{--}	1 mEq/L	2 mEq/L
Osmolality	281 mOsm/L	281 mOsm/L



Body Water

Extracellular (33%)

Intracellular (66%)

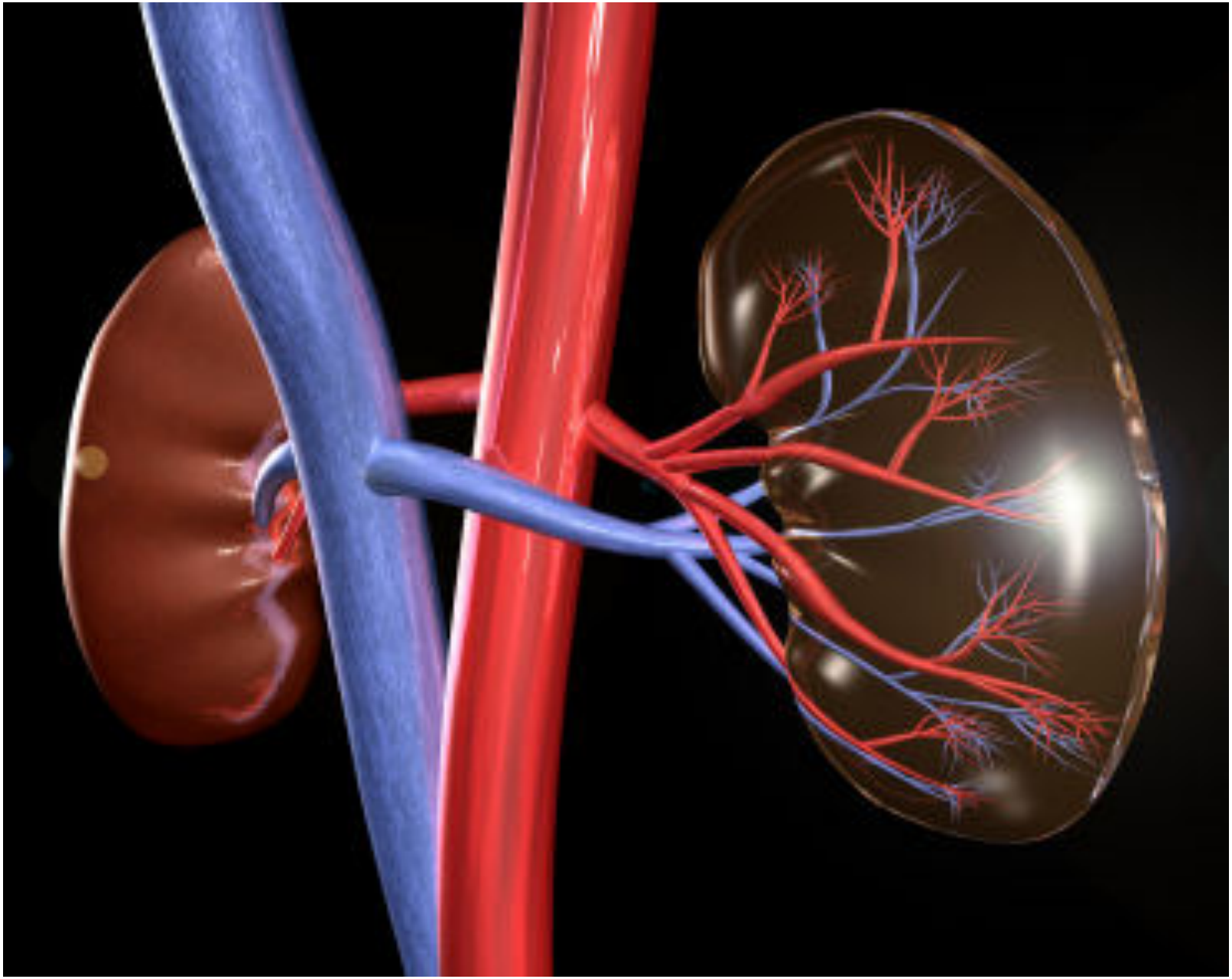
Interstitial (25%)

Plasma (8%)

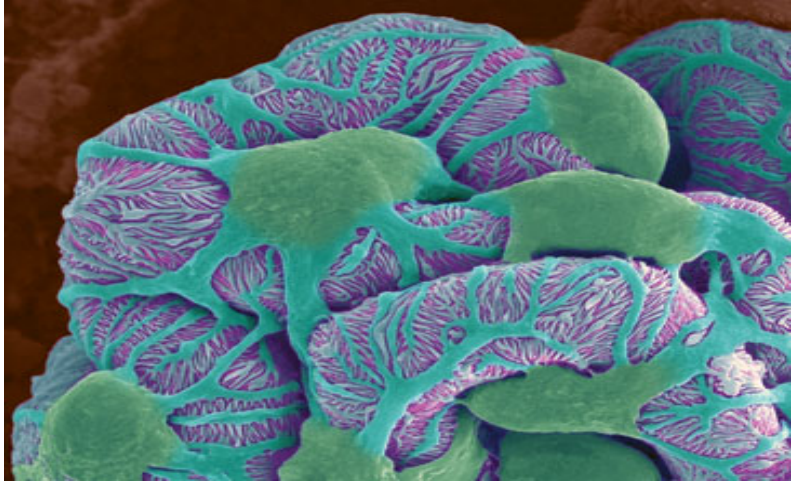
H_2O H_2O

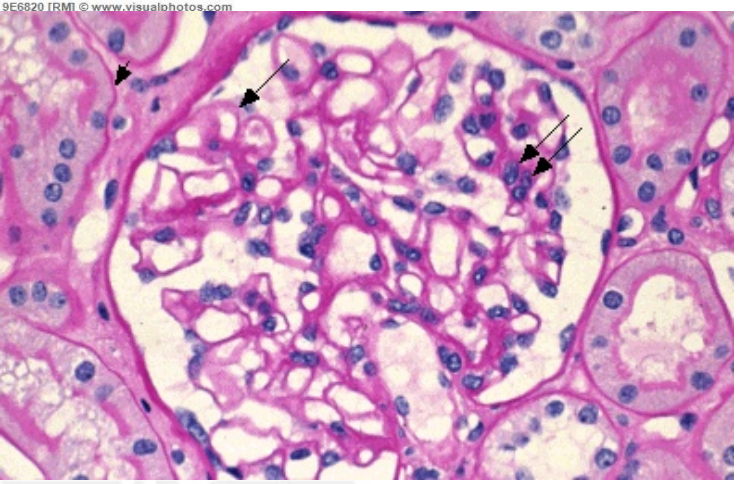
Na Na Na Na

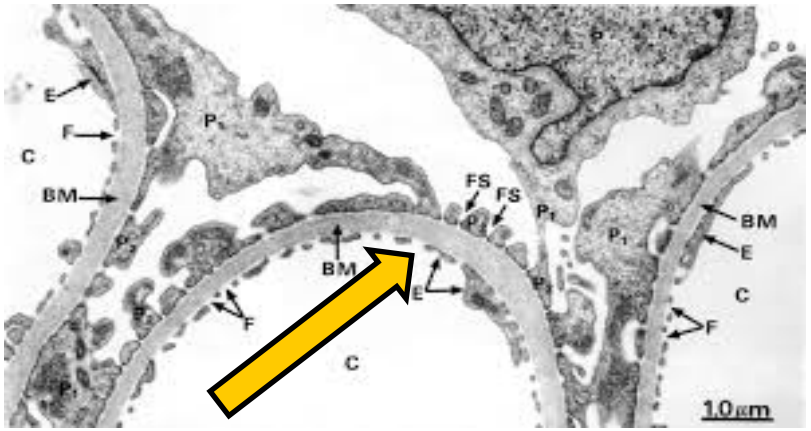
sodio

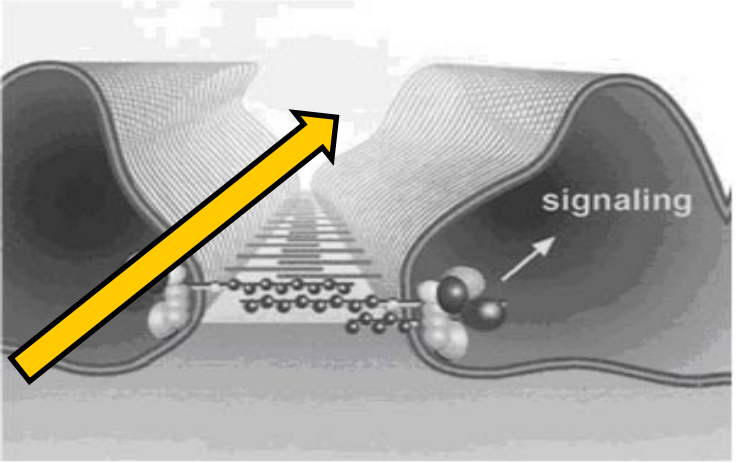


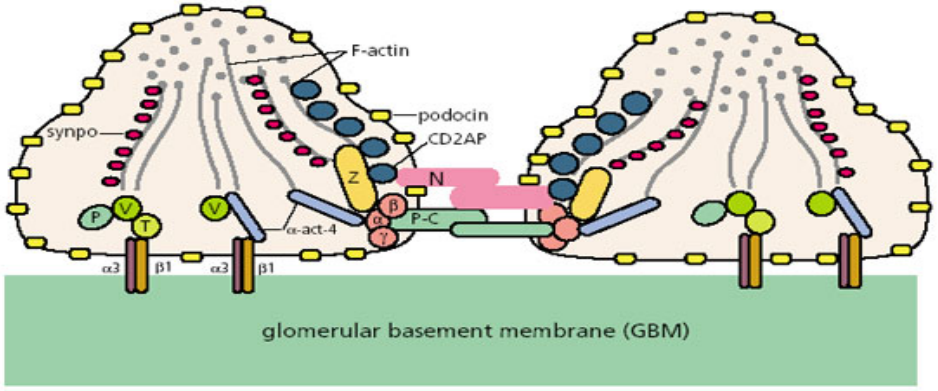

visualphotos.com
9E6820 [RMI © www.visualphotos.com



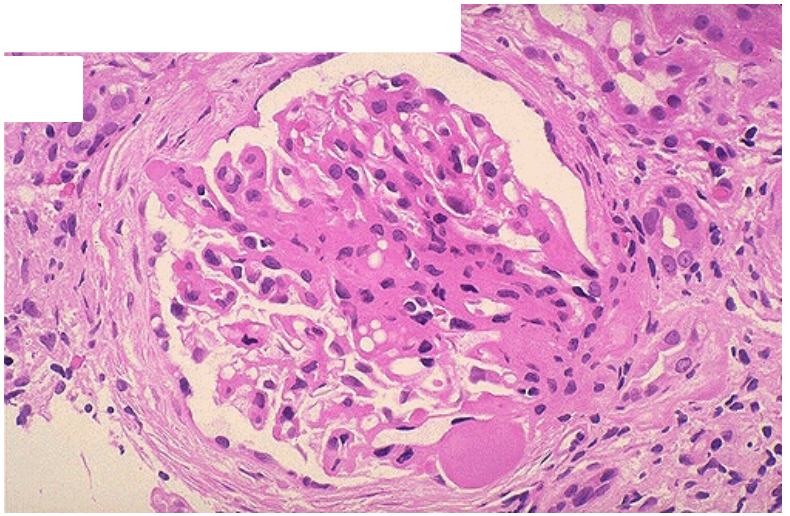


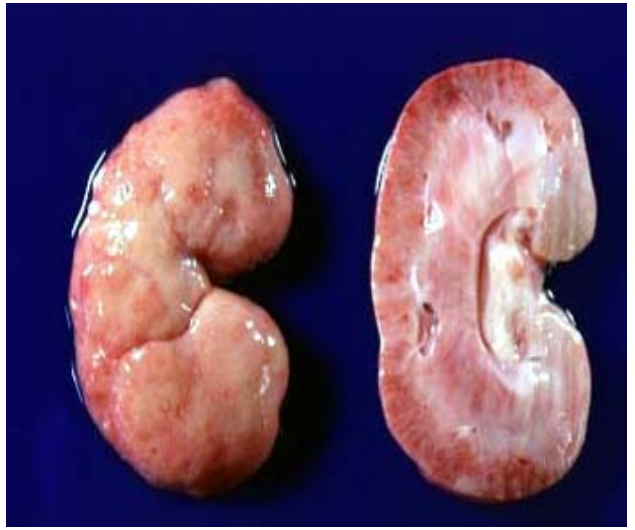

E
F
C
BM
FS
FS
BM
E
C
F
BM
E
C
F
1.0 µm


signaling


F-actin
podocin
CD2AP
synpo
Z
N
P-C
α-act-4
α3
β1
α3
β1
glomerular basement membrane (GBM)


SALT





sodio

SODIO 1

CARACTERÍSTICAS HIGROSOCÓPICAS

ARRASTRE Y SECUESTRO DE AGUA

AUMENTO DEL AGUA Y SODIO CORPORAL TOTAL

AUMENTO DE LA VOLEMIA Y DE LA CARGA DE AGUA Y SOLUTOS FILTRADOS

⇧ ÓXIDO NÍTRICO

HIPERFILTRACIÓN

DAÑO ENDOTELIAL

DAÑO PODOCITARIO

⇩ ÓXIDO NÍTRICO

DAÑO MEMBRANA DE FILTRACIÓN
ESCLEROSIS

PROTEINURIA

ENFERMEDAD RENAL CRÓNICA

sodio

SODIO 2

CARACTERÍSTICAS HIGROSOCÓPICAS

ARRASTRE Y SECUESTRO DE AGUA

AUMENTO DEL AGUA Y SODIO CORPORAL TOTAL

TRASLOCACIÓN CATIÓNICA Na-Ca A NIVEL VASCULAR

AUMENTO DEL TONO VASCULAR

DAÑO ENDOTELIAL RENAL

DAÑO ENDOTELIAL SISTÉMICO

HIPERTENSIÓN ARTERIAL

PROTEINURIA

ENFERMEDAD RENAL CRÓNICA

sodio

SODIO 1 + SODIO 2

AUMENTO DE LA VOLEMIA Y DE LA CARGA DE AGUA Y SOLUTOS FILTRADOS

AUMENTO DEL TONO VASCULAR

HIPERTENSIÓN ARTERIAL

AUMENTO DEL TONO VASCULAR

DAÑO ENDOTELIAL RENAL

DAÑO ENDOTELIAL SISTÉMICO

DAÑO PODOCITARIO

DAÑO MEMBRANA DE FILTRACIÓN
ESCLEROSIS

HIPERTENSIÓN ARTERIAL

HIPERFILTRACIÓN

⇩ ÓXIDO NÍTRICO

PROTEINURIA

ENFERMEDAD RENAL CRÓNICA

AUMENTO DE LA VOLEMIA Y DE LA CARGA DE AGUA Y SOLUTOS FILTRADOS

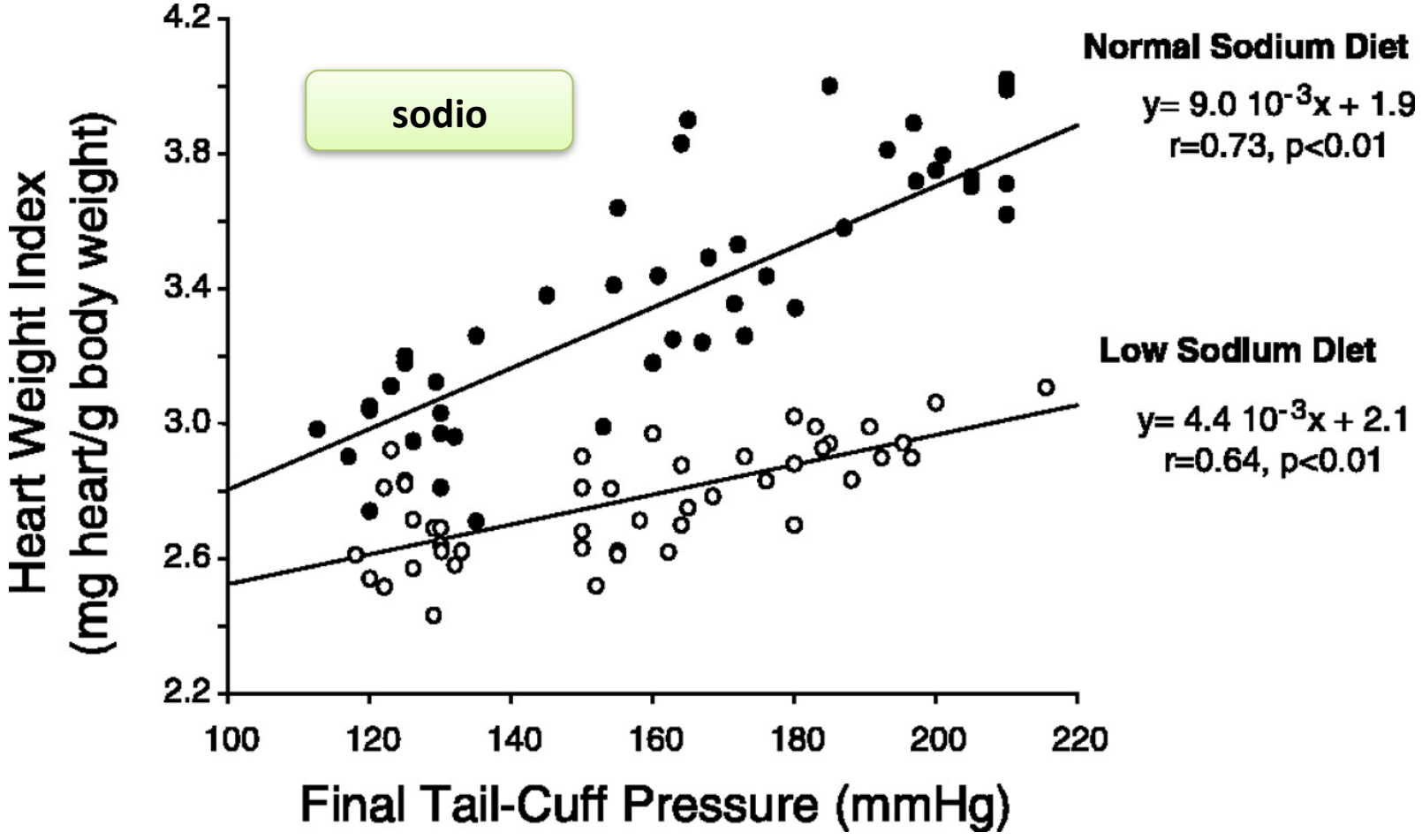
AUMENTO DEL TONO VASCULAR

HIPERTENSIÓN ARTERIAL

DAÑO ENDOTELIAL RENAL

PROTEINURIA

ENFERMEDAD RENAL CRÓNICA



Hiperfiltración glomerular: Aumento absoluto en la Tasa de Filtrado Glomerular (TFG) que ocurre en individuos sanos en respuesta a una carga elevada de proteínas (u otras moléculas con poder osmótico).

Bergström, J. et al. Acta Med. Scand. 1985:;217: 189–196

Este aumento en la TFG es mediada, al menos en parte e inicialmente, por una elevación del óxido nítrico y kalikreínas renales

Pecly, I. M et al Int. J. Clin. Pract. 2006; 60: 1198–1203

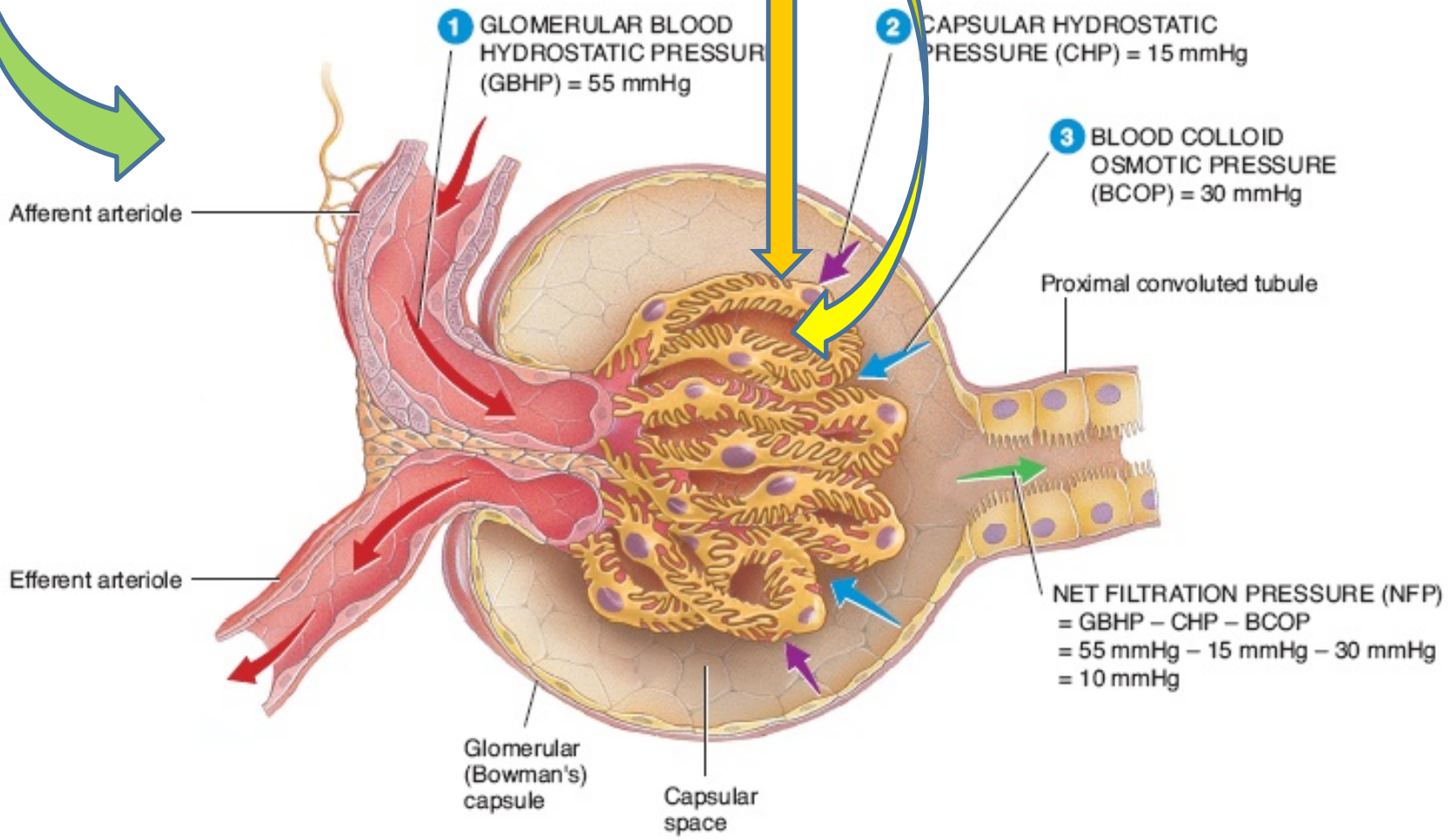
AUMENTO DE LA VOLEMIA Y DE LA CARGA DE AGUA Y SOLUTOS FILTRADOS

A la capacidad de elevar la TFG después de una carga de proteínas se le denomina **RESERVA FUNCIONAL RENAL**.

La pérdida de esta **RESERVA FUNCIONAL RENAL**, y la consecuente hiperfiltración contribuirían en forma directa a la progresión de la enfermedad renal crónica.

Bosch, J. P. Am. J. Med. 1984;77: 873–879 (1984 Helal, I. et al. Nat. Rev. Nephrol. 2012; 8: 293–300

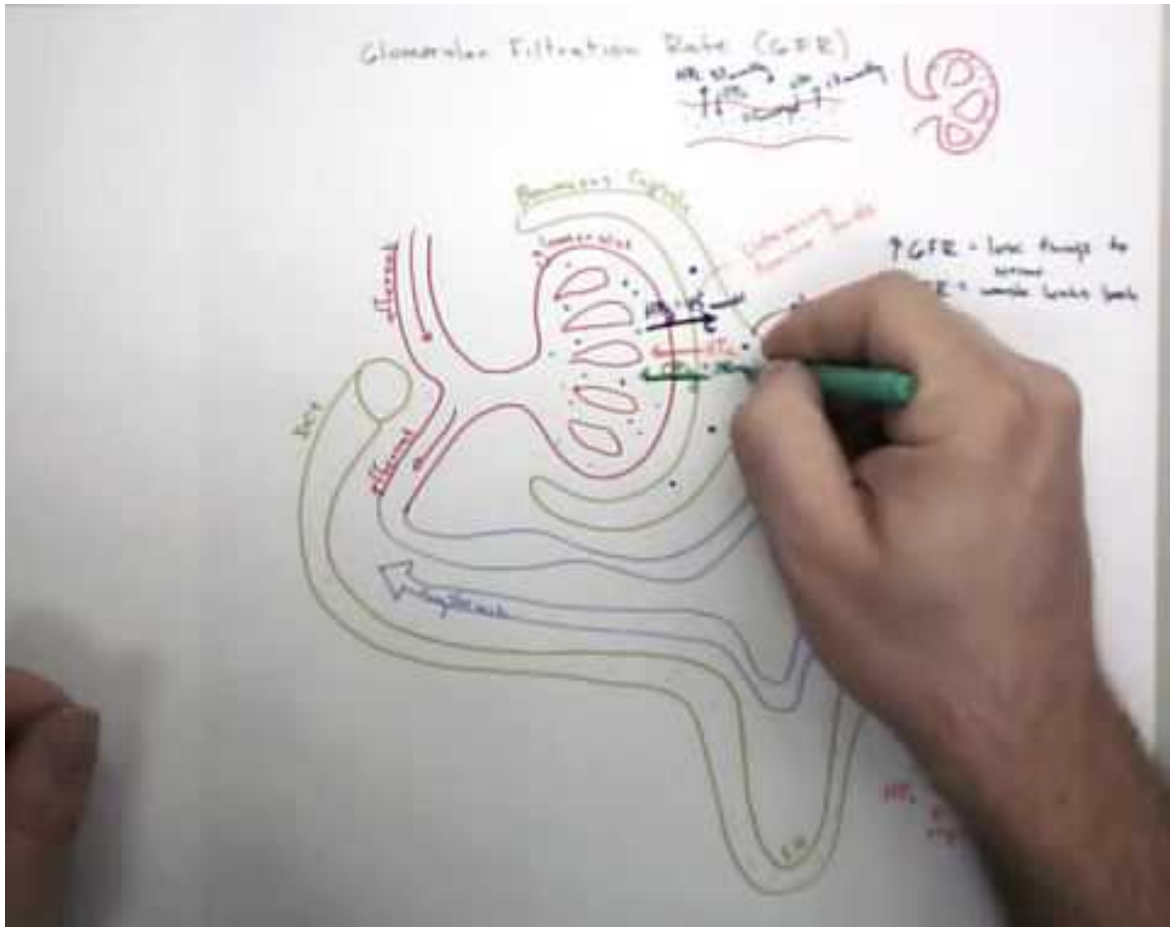
La TFG está determinada por
el flujo plasmático renal,
el gradiente de presión hidráulica a través de la MBG
y el coeficiente de ultrafiltración



Helal, I. *et al. Nat. Rev. Nephrol. 2012; 8: 293–300*

La hiperfiltración glomerular se define como un aumento en la fracción de filtrado glomerular (FF)

Huang, S. H. et al. Clin. J. Am. Soc. Nephrol. 2011; 6: 274–280



FF= VFG/FPR
FF normal: 18.7 ± 3.2%.17

En 1981, Brenner et al. demostraron que el deterioro progresivo de la función renal era el resultado de cambios hemodinámicos glomerulares compensatorios que ocurrían en respuesta a la pérdida de la masa renal.

Brenner, B. M., et al. Acta Endocrinol. Suppl. (Copenh.) 1981; 242: 7–10

Brenner, B. M., et al Kidney Int. 1996;49: 1774–1777

En modelos experimentales de reducción de la masa renal, las nefronas remanentes desarrollaban hipertrofia, asociada a una resistencia arteriolar reducida y un aumento en el flujo sanguíneo renal.

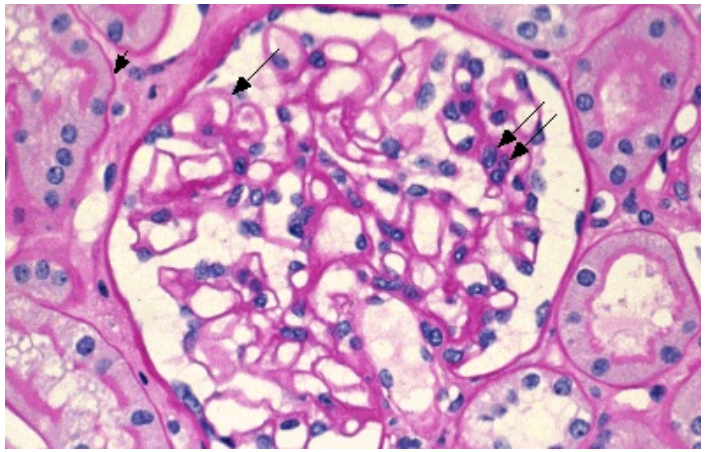
↑ ÓXIDO NÍTRICO

La resistencia arteriolar aferente disminuía más que la resistencia arteriolar eferente con la progresión de la enfermedad renal.

Hostetter, T. H. et al Am. J. Physiol. 1981;241: F85–F93

DAÑO ENDOTELIAL ⇔ **DAÑO PODOCITARIO**

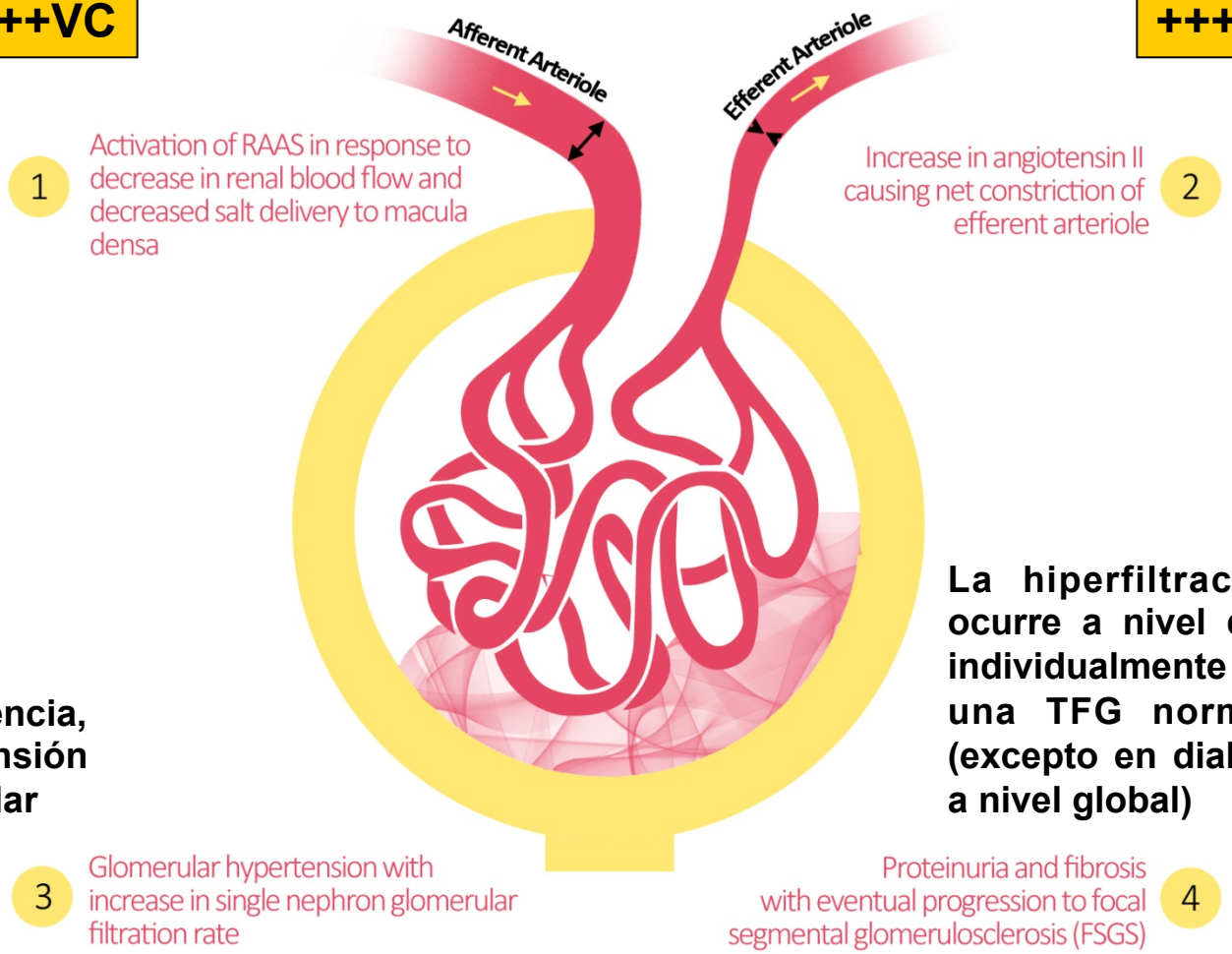
↓ ÓXIDO NÍTRICO



HIPERFILTRACIÓN

++VC

++++VC



Como consecuencia, aparece hipertensión intraglomerular

La hiperfiltración glomerular ocurre a nivel de cada nefrona individualmente y se asocia con una TFG normal o reducida (excepto en diabetes, que se da a nivel global)

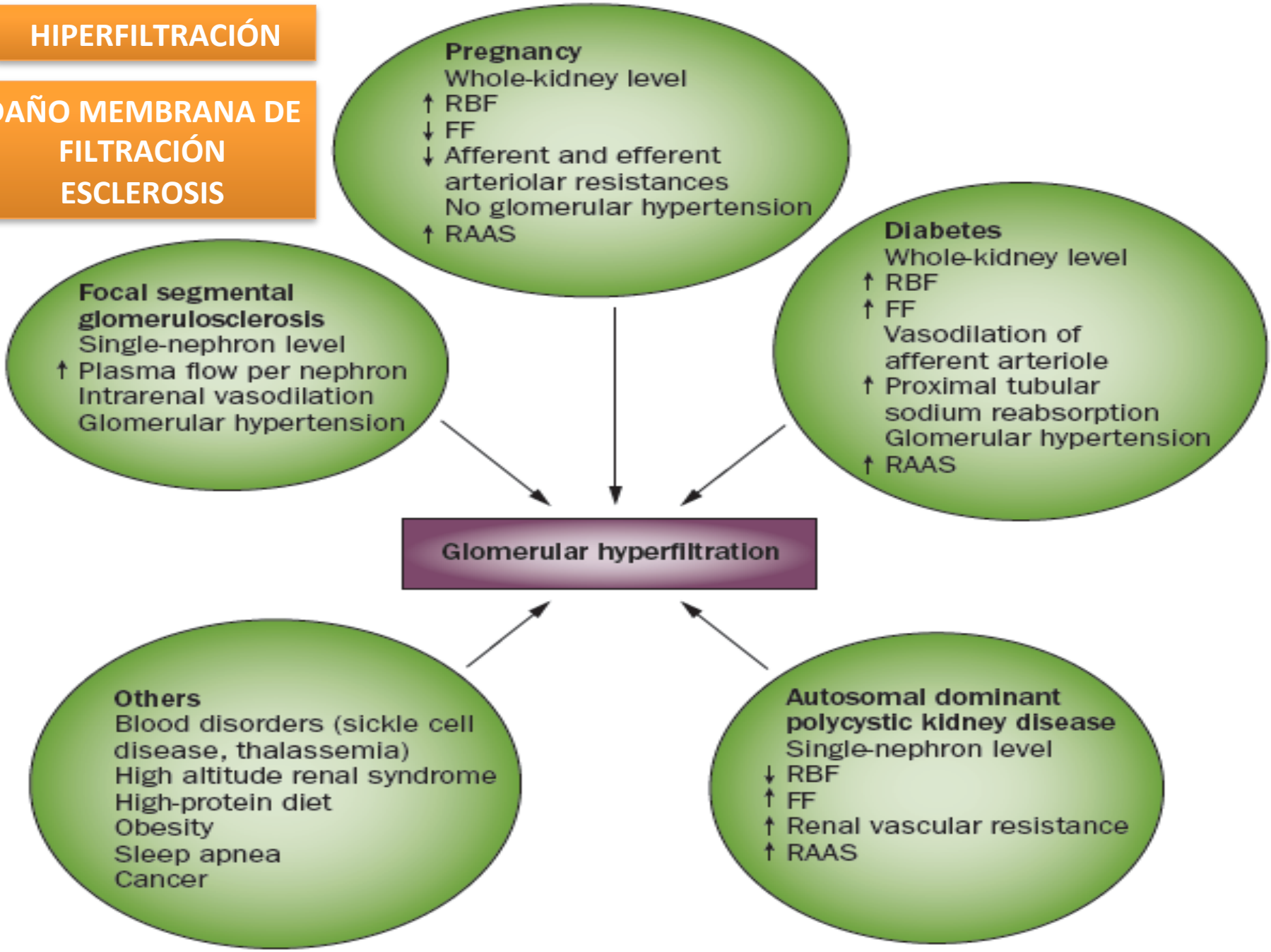
Neuringer, J. R. et al J. Hypertens. Suppl. 1992; 10: S91–S97

Neuringer, J. R. et al Am. J. Kidney Dis. 1993;22: 98–104

HIPERFILTRACIÓN

DAÑO MEMBRANA DE FILTRACIÓN

ESCLEROSIS



Helal, I. *et al. Nat. Rev. Nephrol. 2012; 8: 293–300*

HIPERFILTRACIÓN

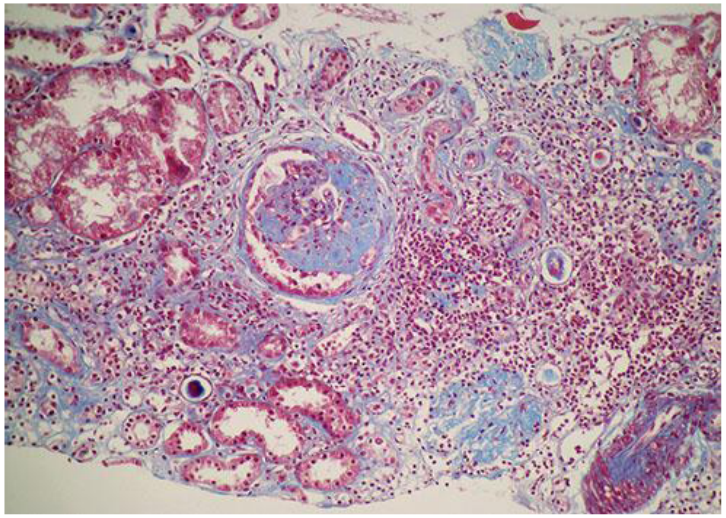
Hiperfiltración glomerular en la esclerosis FSGS

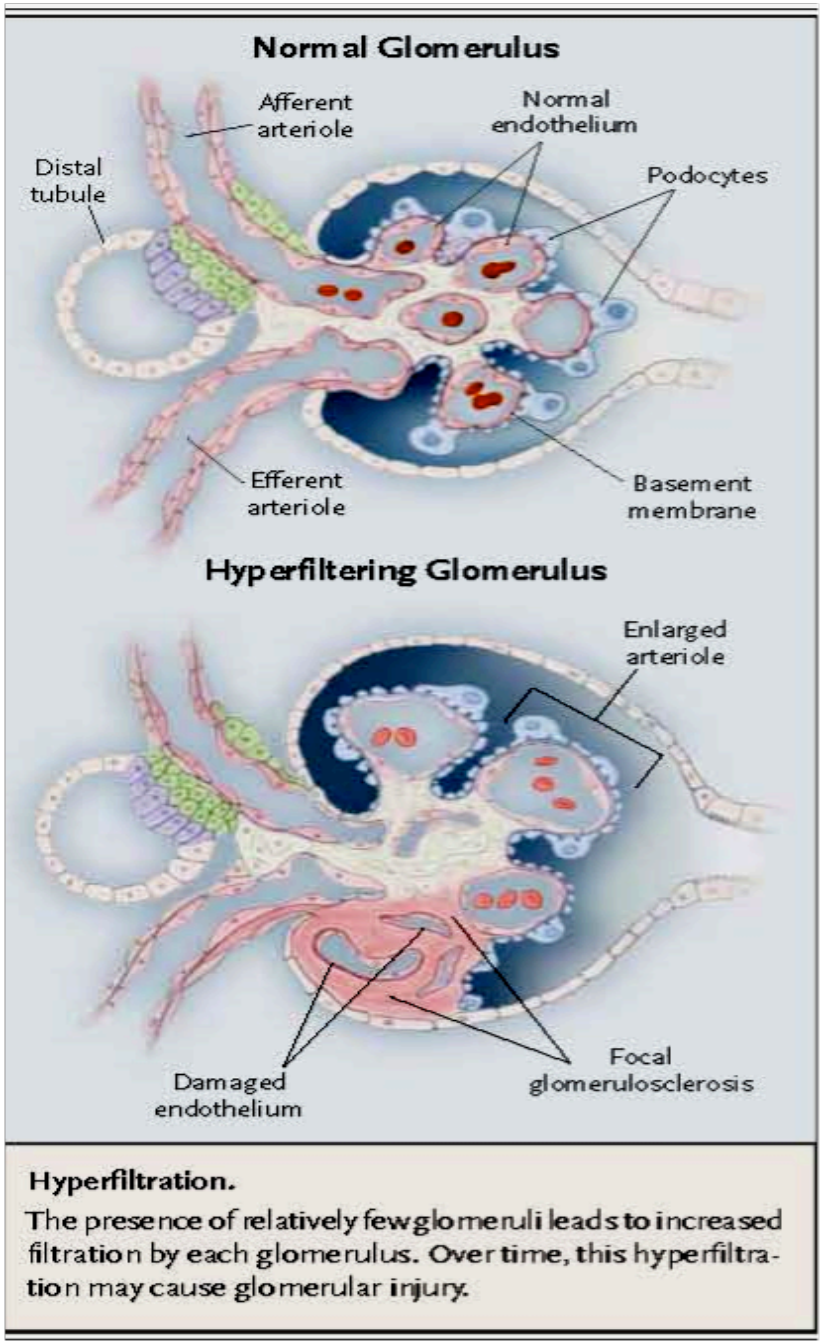
PRIMARIA: GENÉTICA – mutaciones en proteínas

ADQUIRIDA – factores de permeabilidad

DAÑO MEMBRANA DE FILTRACIÓN ESCLEROSIS

SECUNDARIA: masa renal reducida
reflujo vésicoureteral
Obesidad
HIV, drogas, etc
Como resultado de un daño glomerular primario





Hyperfiltration.
The presence of relatively few glomeruli leads to increased filtration by each glomerulus. Over time, this hyperfiltration may cause glomerular injury.

Podocyte injury in focal segmental glomerulosclerosis: Lessons from animal models (a play in five acts)

VD D'Agati[1]

Kidney International (2008) **73,** 399–406; doi:10.1038/sj.ki.5002655;

Case Reports in Nephrology and Urology

Case Rep Nephrol Urol 2013;3:51–57

DOI: 10.1159/000351516
Published online: May 4, 2013

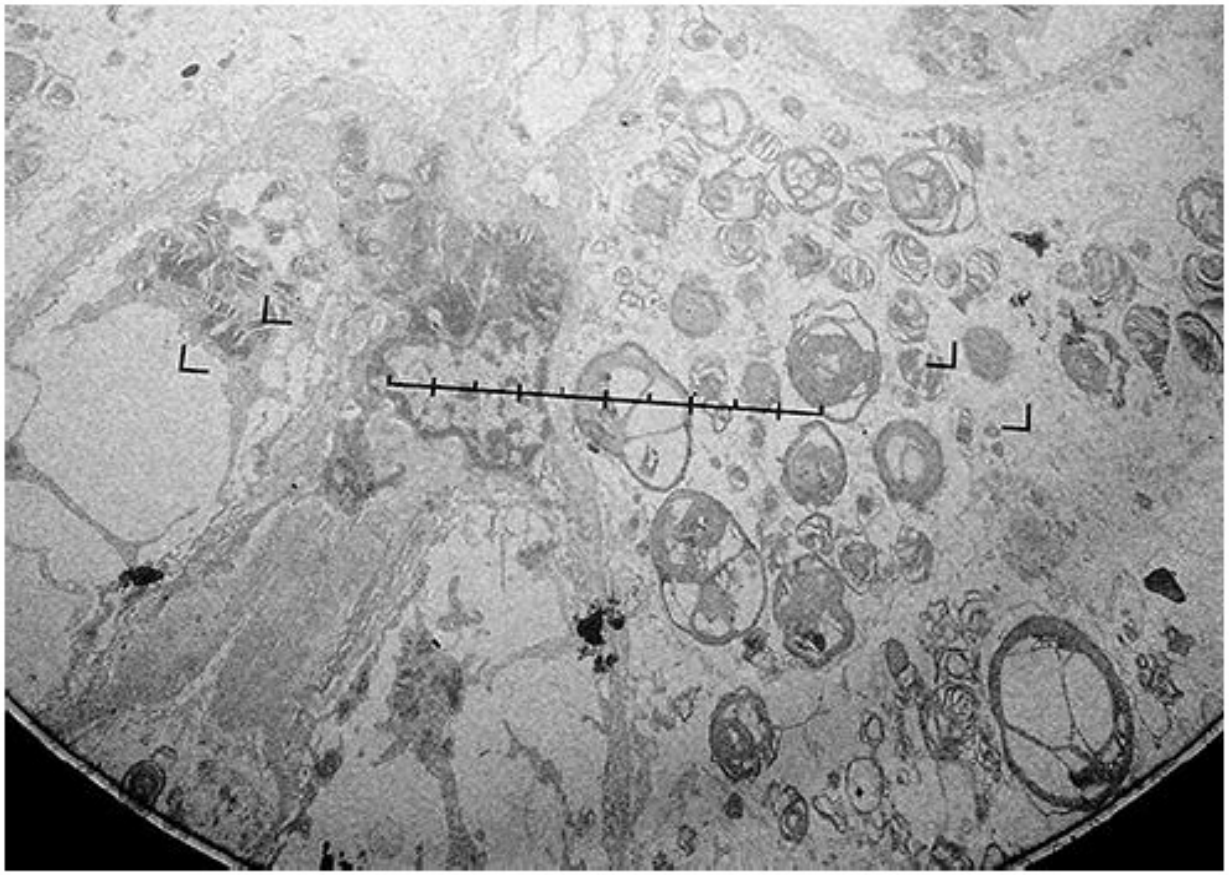
Initially Nondiagnosed Fabry's Disease when Electron Microscopy Is Lacking: The Continuing Story of Focal and Segmental Glomerulosclerosis

H. Trimarchi[a] A. Karl[a] M.S. Raña[a] M. Forrester[a] V. Pomeranz[a]
F. Lombi[a] A. Iotti[b]

[a]Nephrology Service and [b]Histopathology Service, Hospital Británico, Buenos Aires, Argentina

ACT 1: SEEING IS BELIEVING: ULTRASTRUCTURAL STUDIES PROVIDE MECHANISTIC INSIGHTS

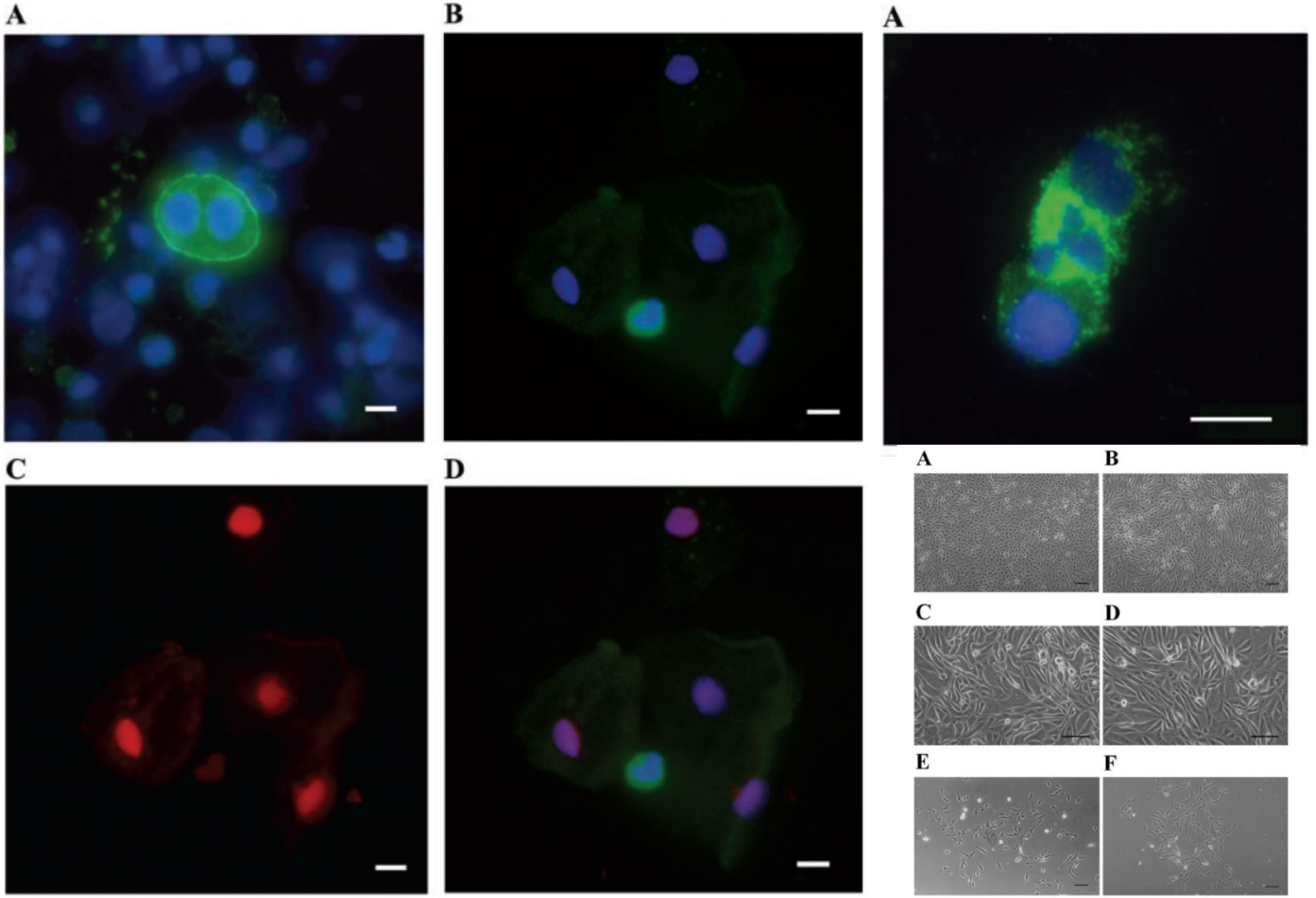
Kidney International (2008) **73,** 399–406; doi:10.1038/sj.ki.5002655;



Case Rep Nephrol Urol 2013;3:51–57

DOI: 10.1159/000351516

ACT 2: GOING, GOING, GONE… THE ROLE OF PODOCYTE DEPLETION

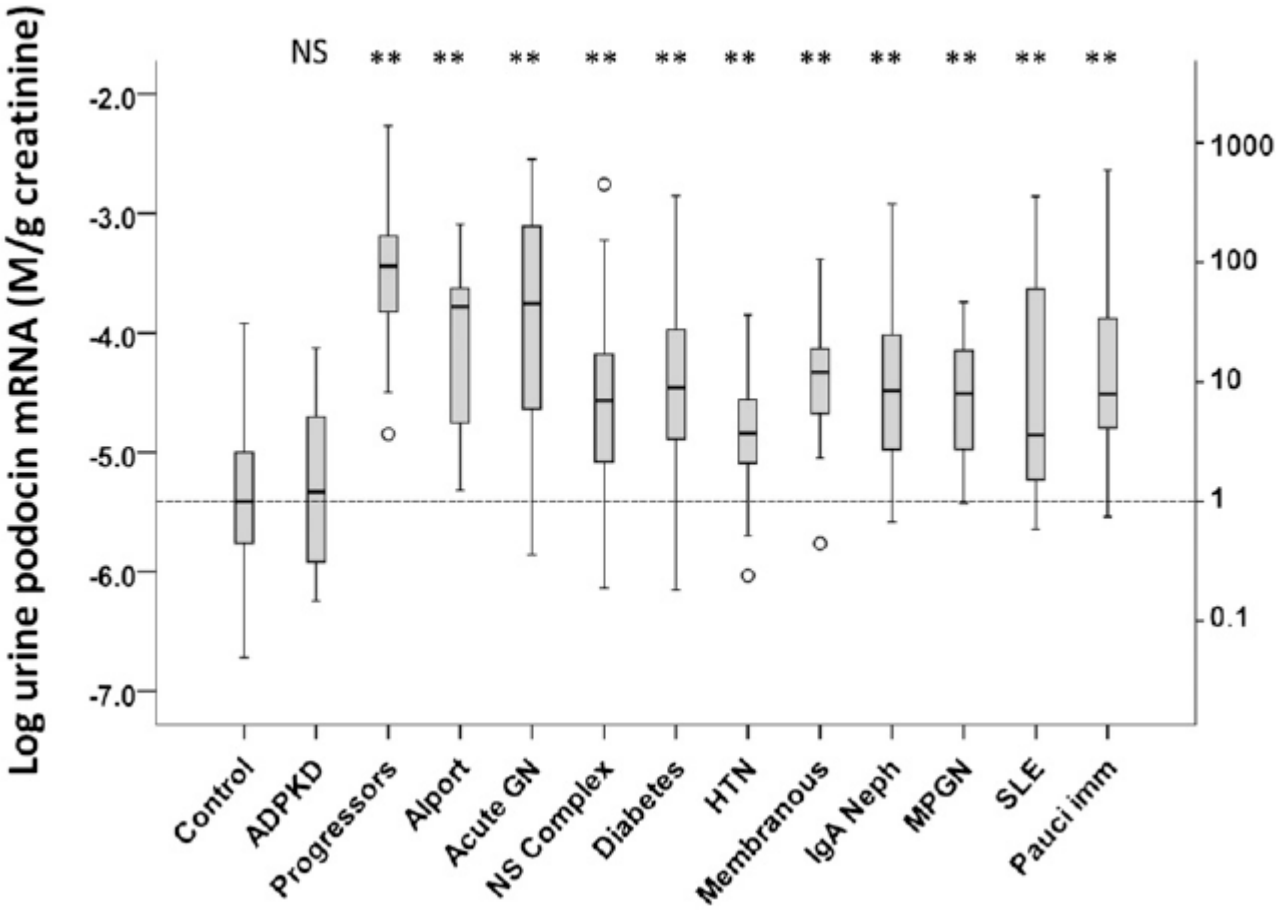


Vogelmann et al.

Am J Physiol Renal Physiol. 2003 July ; 285(1): F40–F48.

Urine Podocyte mRNAs, Proteinuria, and Progression in Human Glomerular Diseases

Larysa Wickman,* Farsad Afshinnia,† Su Q. Wang,† Yan Yang,† Fei Wang,‡ Mahboob Chowdhury,† Delia Graham,* Jennifer Hawkins,† Ryuzoh Nishizono,† Marie Tanzer,* Jocelyn Wiggins,† Guillermo A. Escobar,§ Bradley Rovin,‖ Peter Song,‡ Debbie Gipson,* David Kershaw,* and Roger C. Wiggins†



J Am Soc Nephrol **24:** 2081–2095, 2013

ACT 3: PROOF OF CONCEPT: ANIMAL MODELS AND THE GENETIC BASIS OF FSGS

Kidney International (2008) **73,** 399–406; doi:10.1038/sj.ki.5002655;

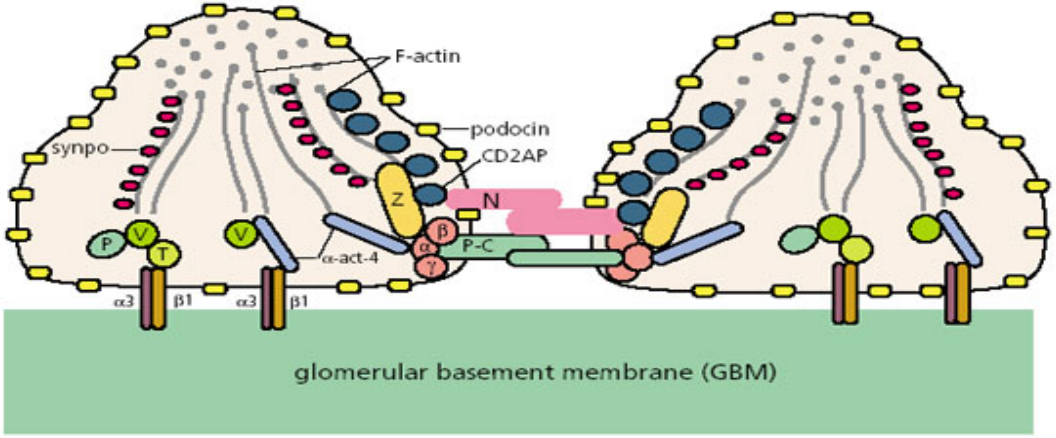
Online Submissions: http://www.wjgnet.com/esps/
wjnephrol@wjgnet.com
doi:10.5527/wjn.v2.i4.103

World J Nephrol 2013 November 6; 2(4): 103-110
ISSN 2220-6124 (online)

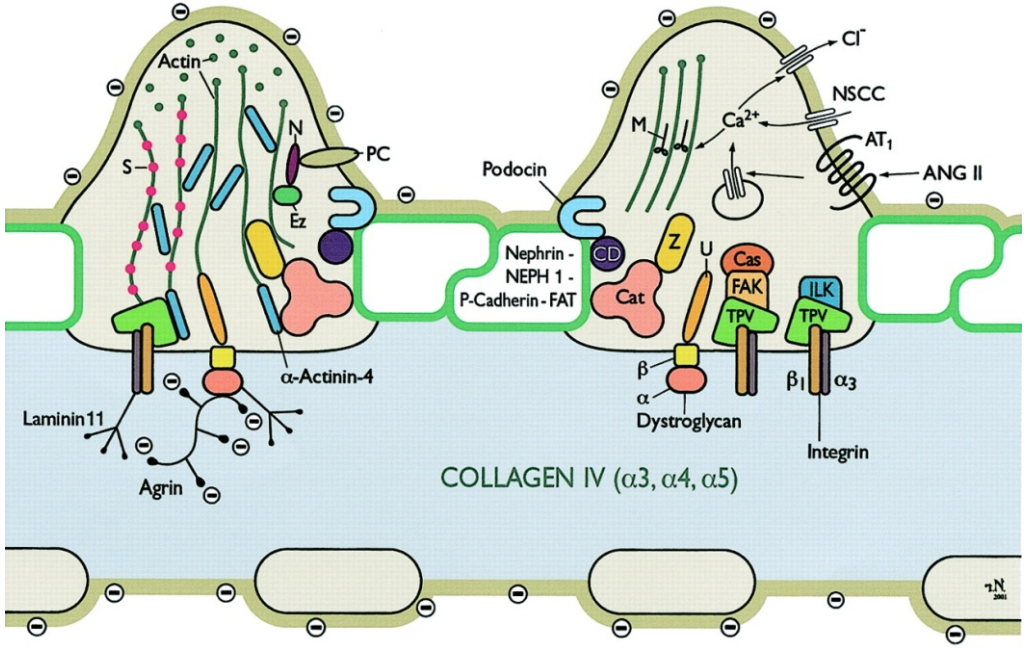
REVIEW

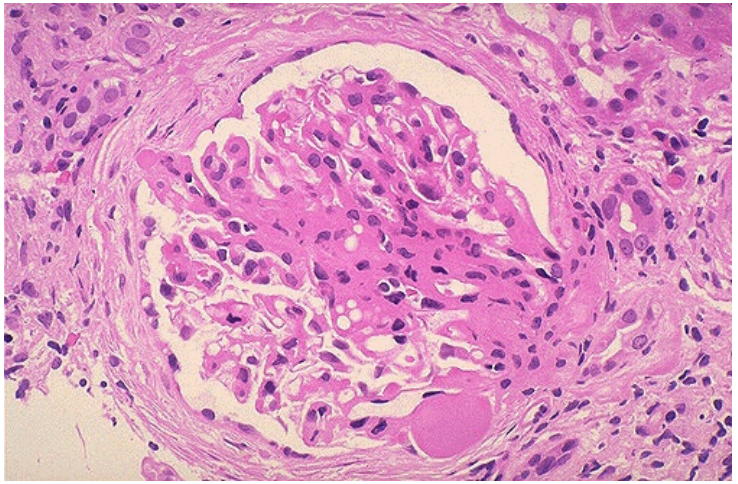
Primary focal and segmental glomerulosclerosis and soluble factor urokinase-type plasminogen activator receptor

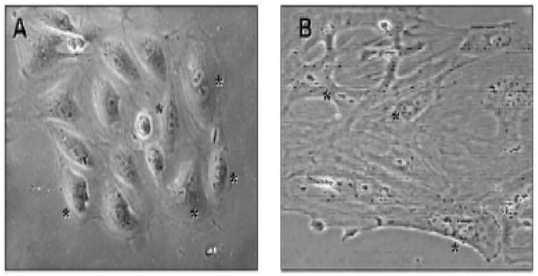
Hernán Trimarchi

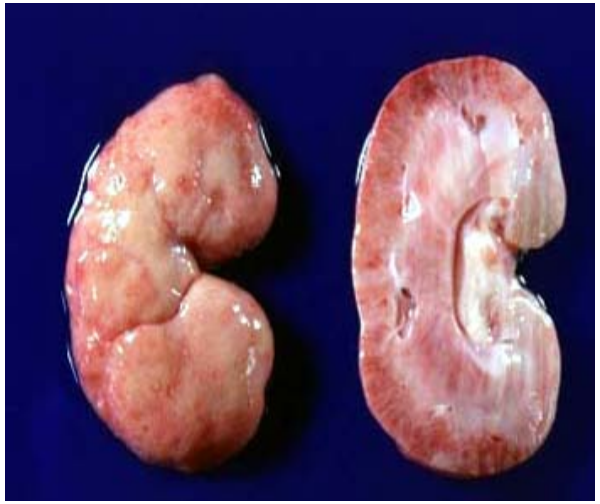


ACT 4: MORE IS NOT NECESSARILY BETTER: PODOCYTE DYSREGULATION









Iney International (2008) **73,** 399–406; doi:10.1038/sj.ki.5002655;

ACT 5: THE MISSING LINK: HOW IRREVERSIBLE FOOT PROCESS EFFACEMENT AND PODOCYTE LOSS PROMOTE GLOMERULOSCLEROSIS

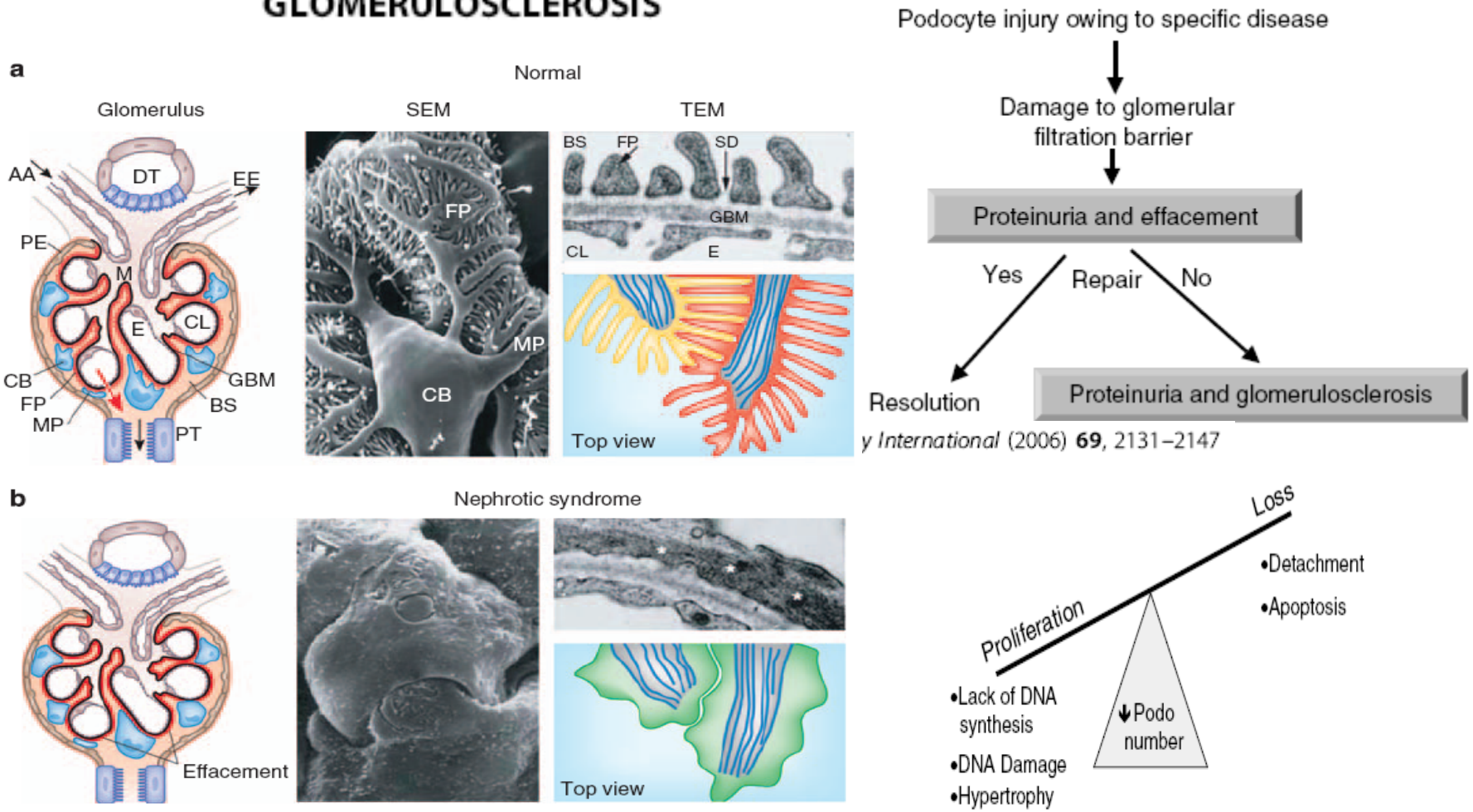
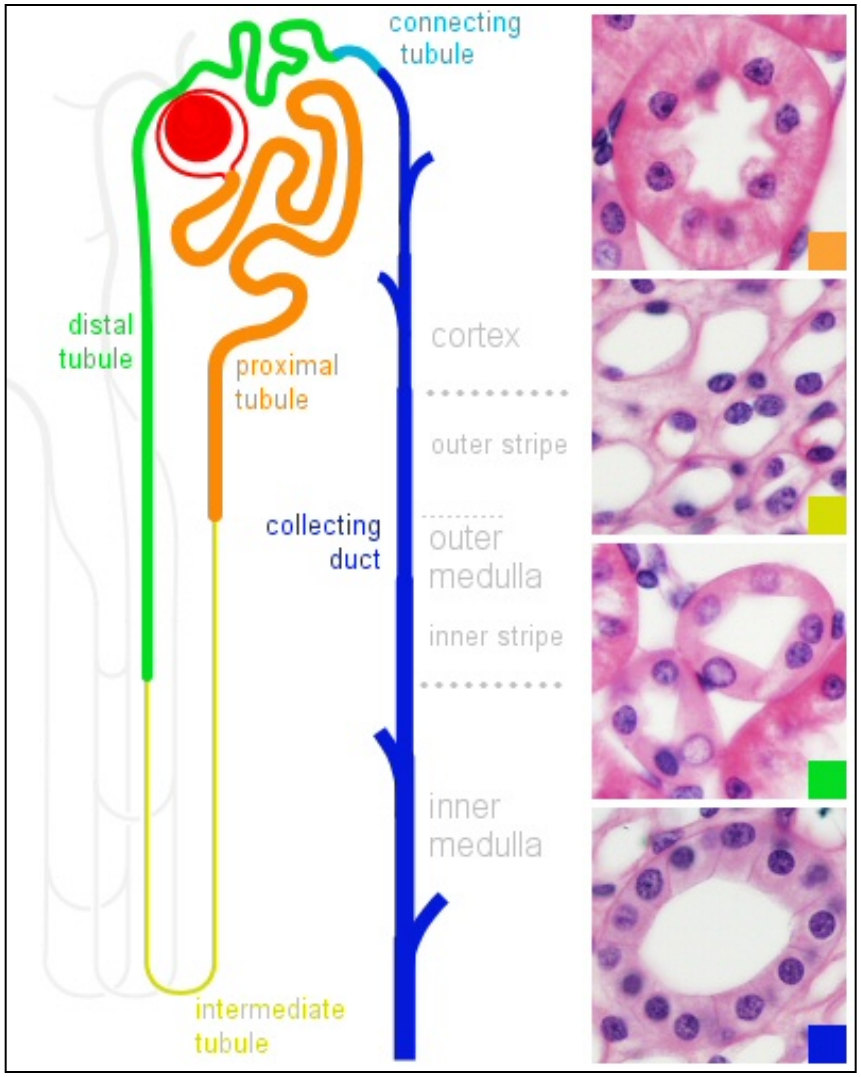


Figure 2 | Factors governning podocyte number. Total podocyte (podo) number is a balance between proliferation and loss. Podocyte number is reduced by either a decrease in proliferation owing to lack of DNA synthesis, DNA damage or hypertrophy, and/or an in crease in podocyte loss owing to detachment and apoptosis.



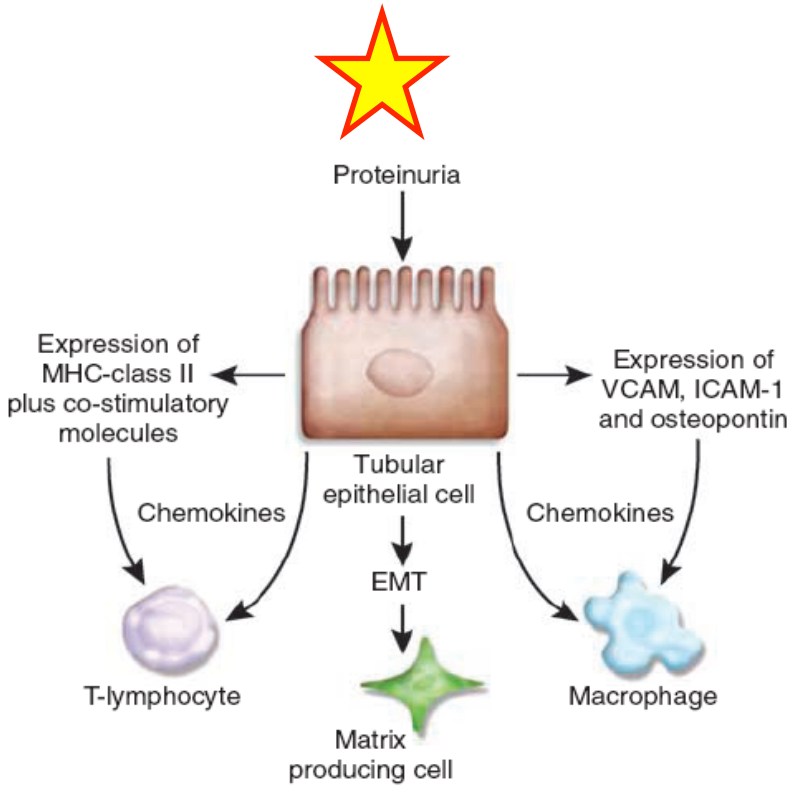


Figure 1 | Effects of proteinuria on tubular epithelial cells. Increased protein absorption by tubular cells may result in direct tubular toxicity, release of chemokines and cytokines, increased expression of adhesion and MHC class II molecules along with co-stimulatory molecules. The net effect is an increased influx of mononuclear inflammatory cells. The evidence for direct proteinuria induced EMT is weak.

Proteinuria – What component of the barrier is responsible?

The podocyte,

Glomerular basement membrane,

Fenestrated endothelium, or the

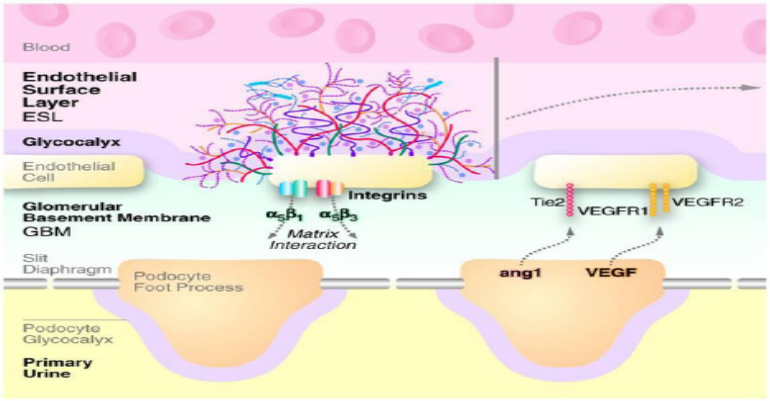
Endothelial surface layer?

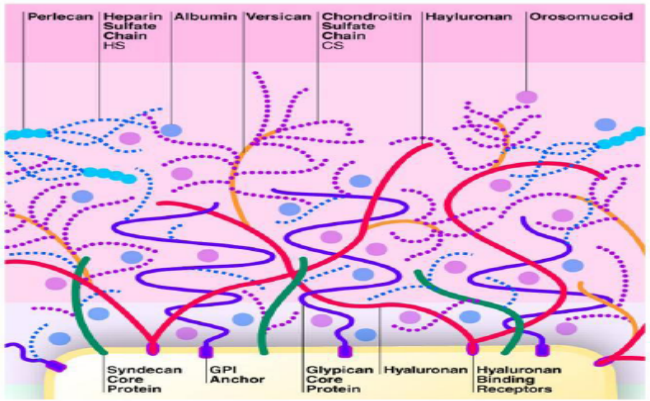
The correct answer is probably – All of the above!

The Sahlgrenska Academy

UNIVERSITY OF GOTHENBURG

Glomerular endothelial cell surface layer





Haraldsson, Nyström & Deen. Properties of the glomerular barrier and mechanisms of proteinuria. Physiol. Rev. 88: 451-487 2008;

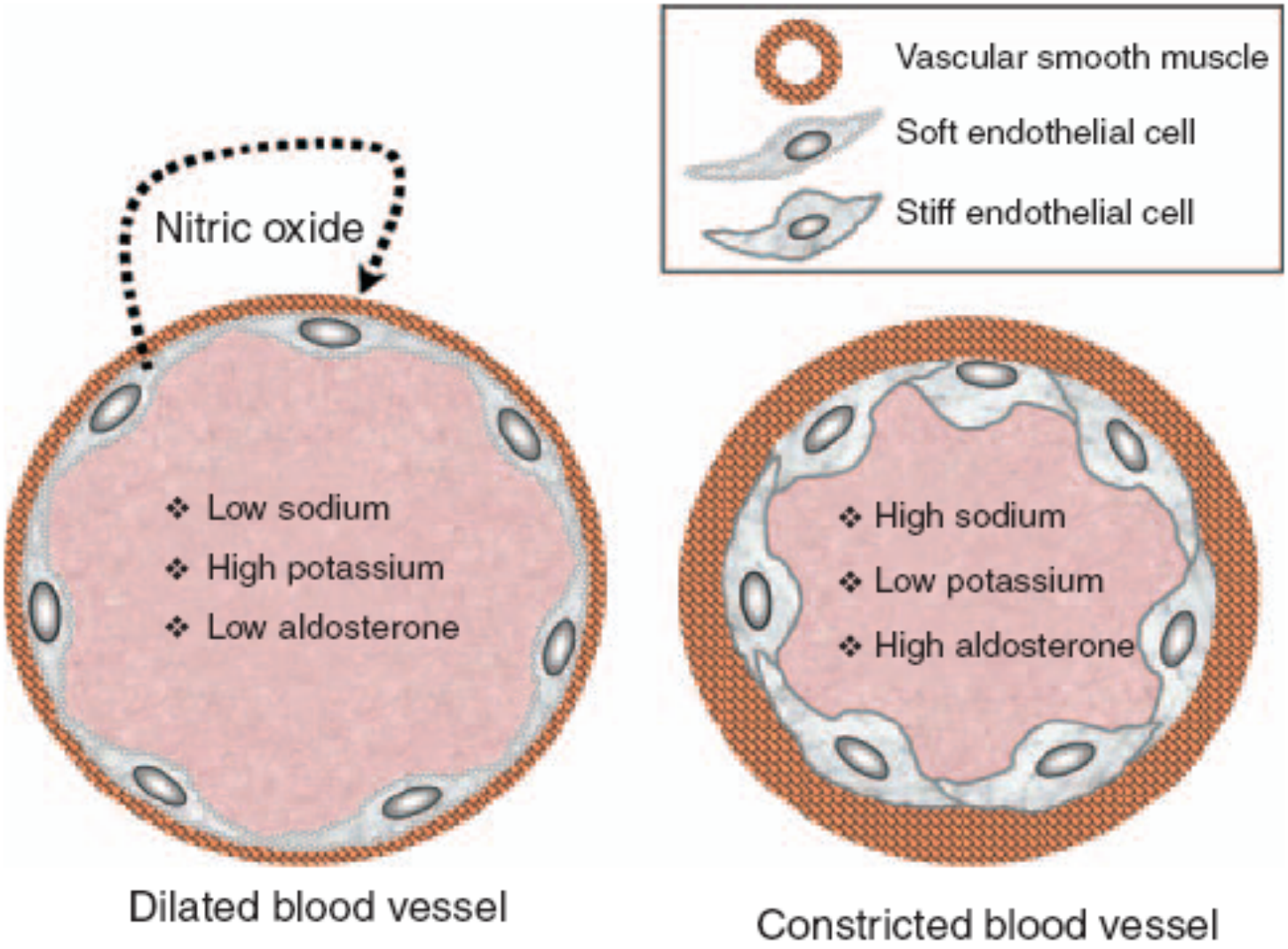


Figure 6 | Concept of how sodium, potassium, and aldosterone contribute to the regulation of blood vessel tone.

Kidney International 2010; 77: 490–494

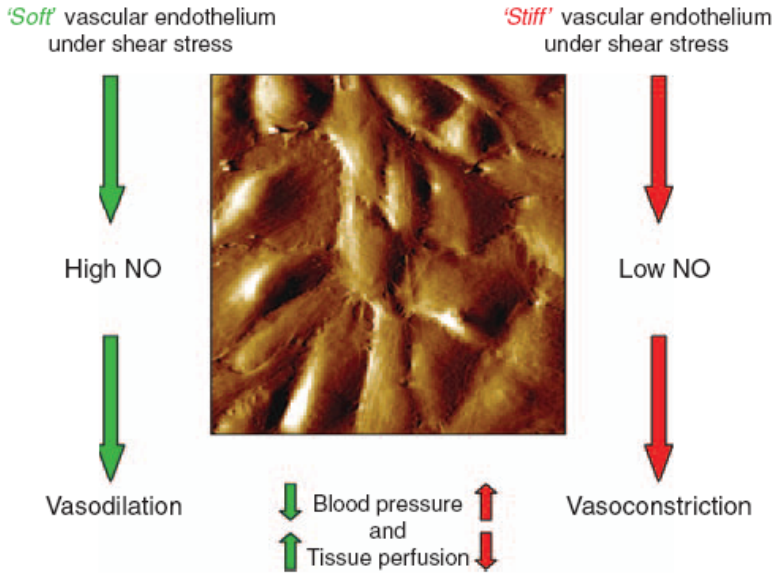


Figure 1 | Concept of how the mechanical stiffness of endothelial cells participates in the regulation of blood pressure.

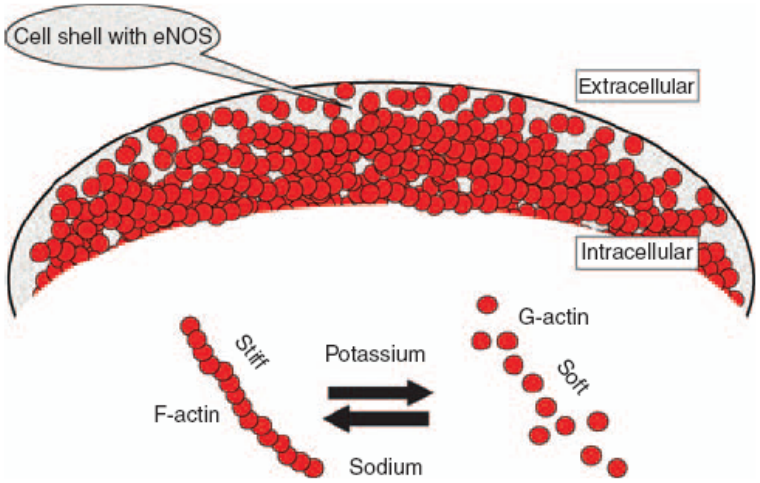


Figure 5 | Hypothesis for how sodium and potassium control the fluidity of the cortical zone ('cell shell') in an endothelial cell.

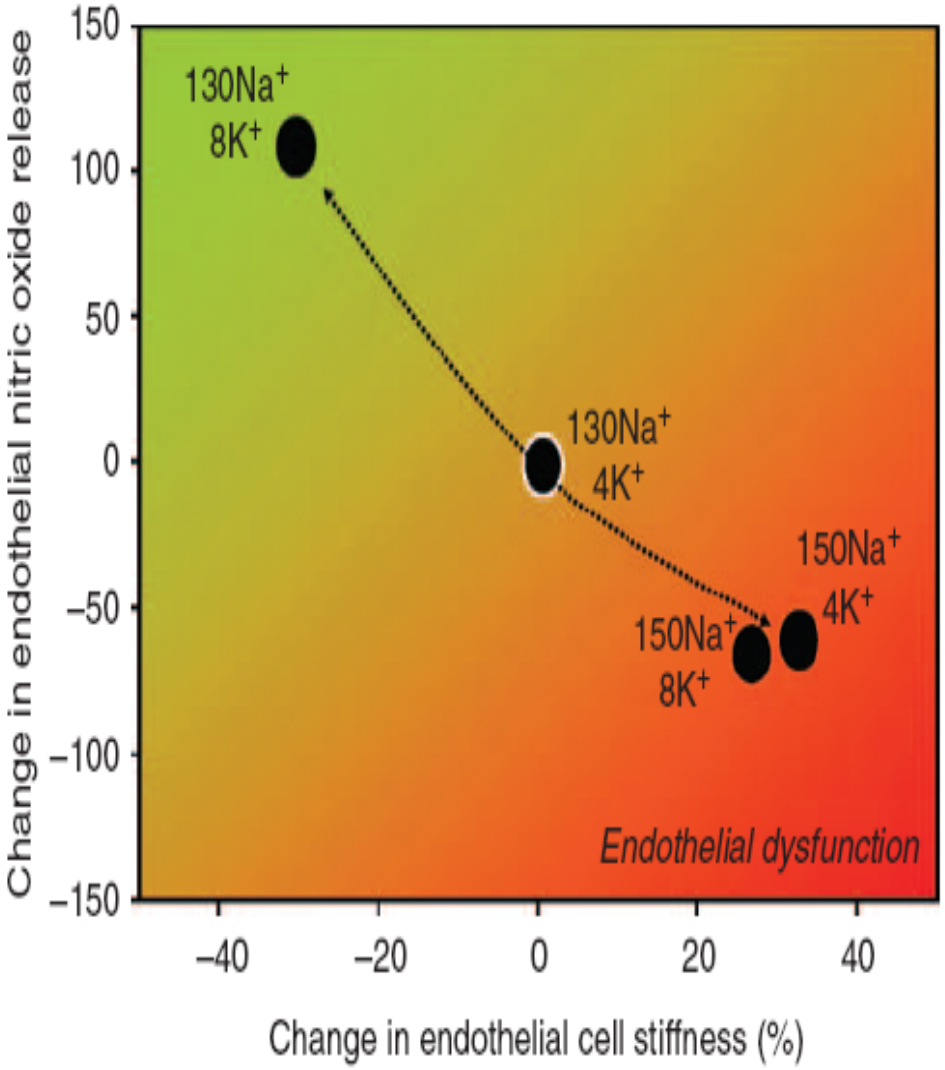
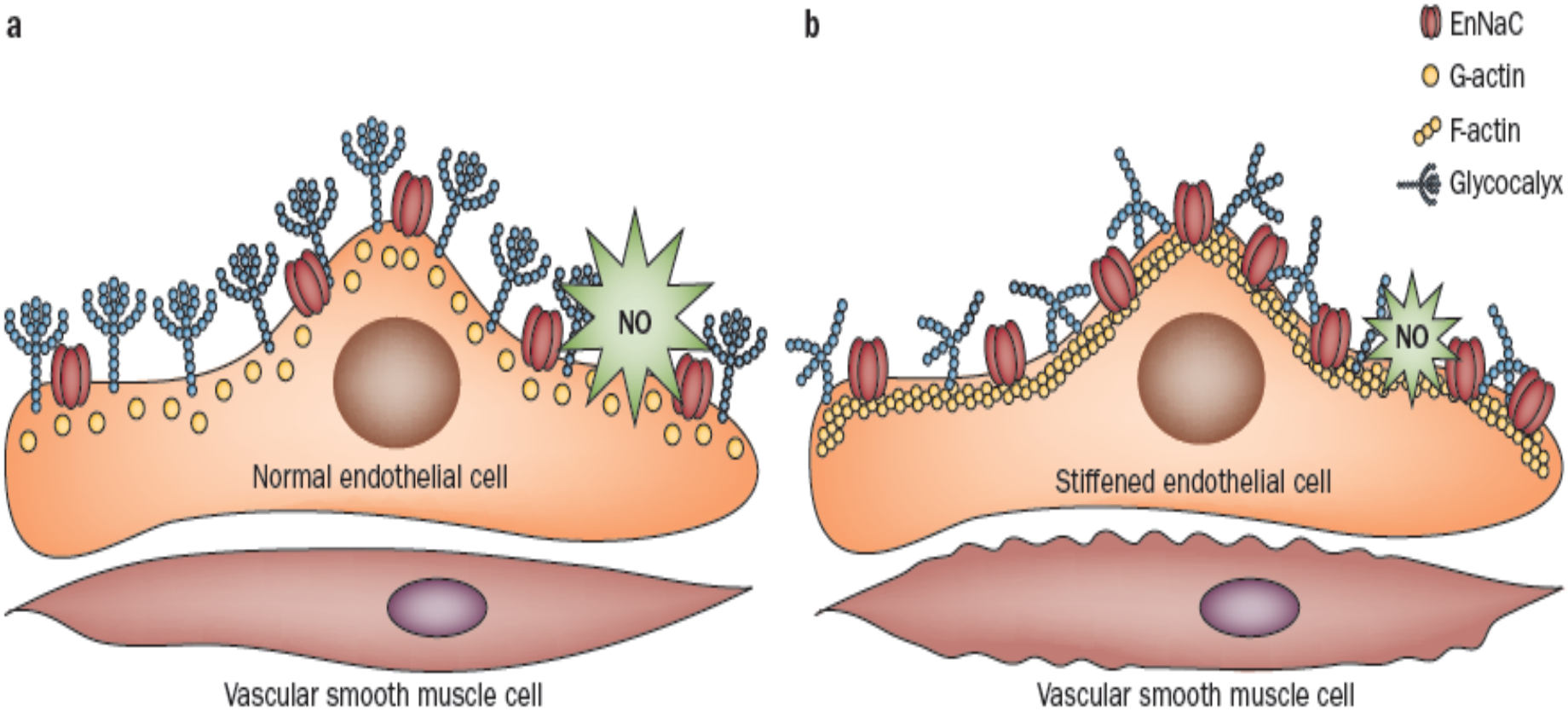


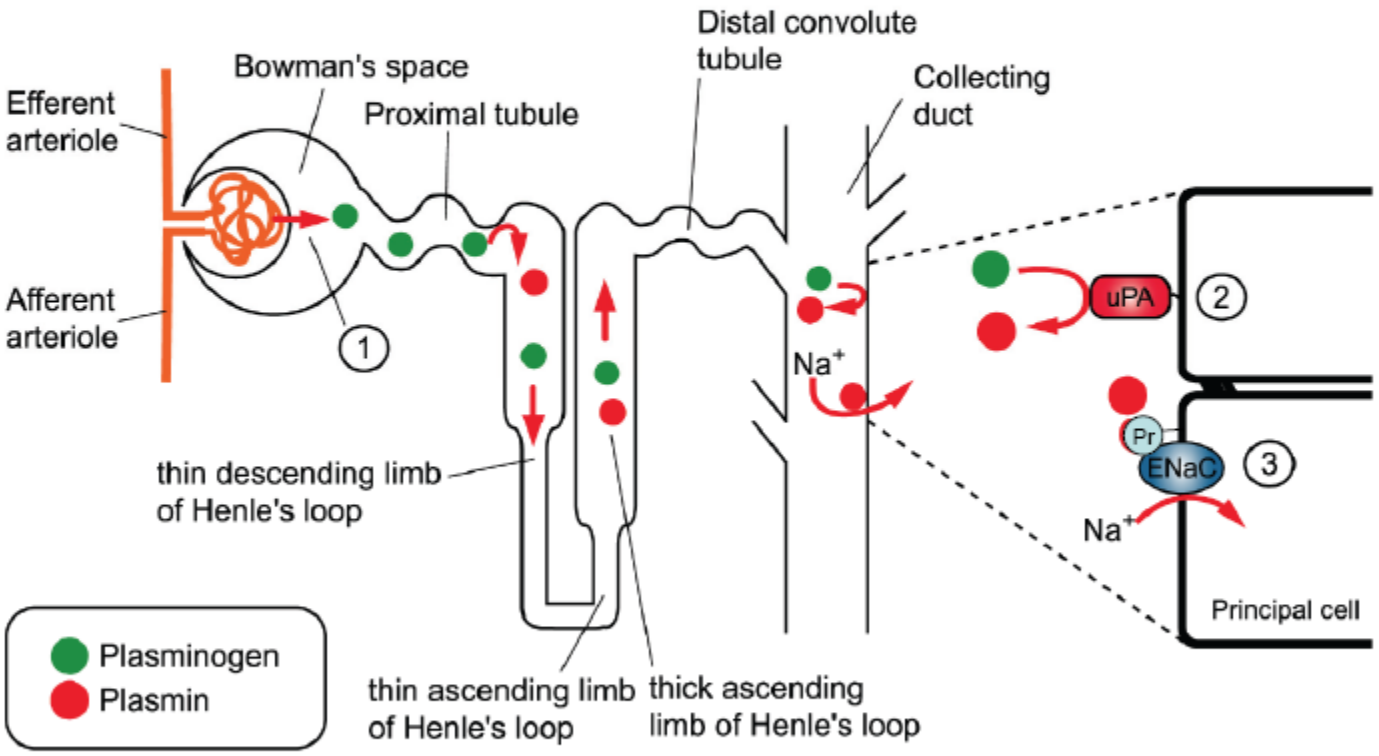
Figure 4 | Negative correlation between cell stiffness and nitric oxide (NO) release. NO release was derived from the nitrite concentrations measured in the supernatant culture media. Data were taken from Oberleithner *et al.*[9,15]

Blood pressure and amiloride-sensitive sodium channels in vascular and renal cells



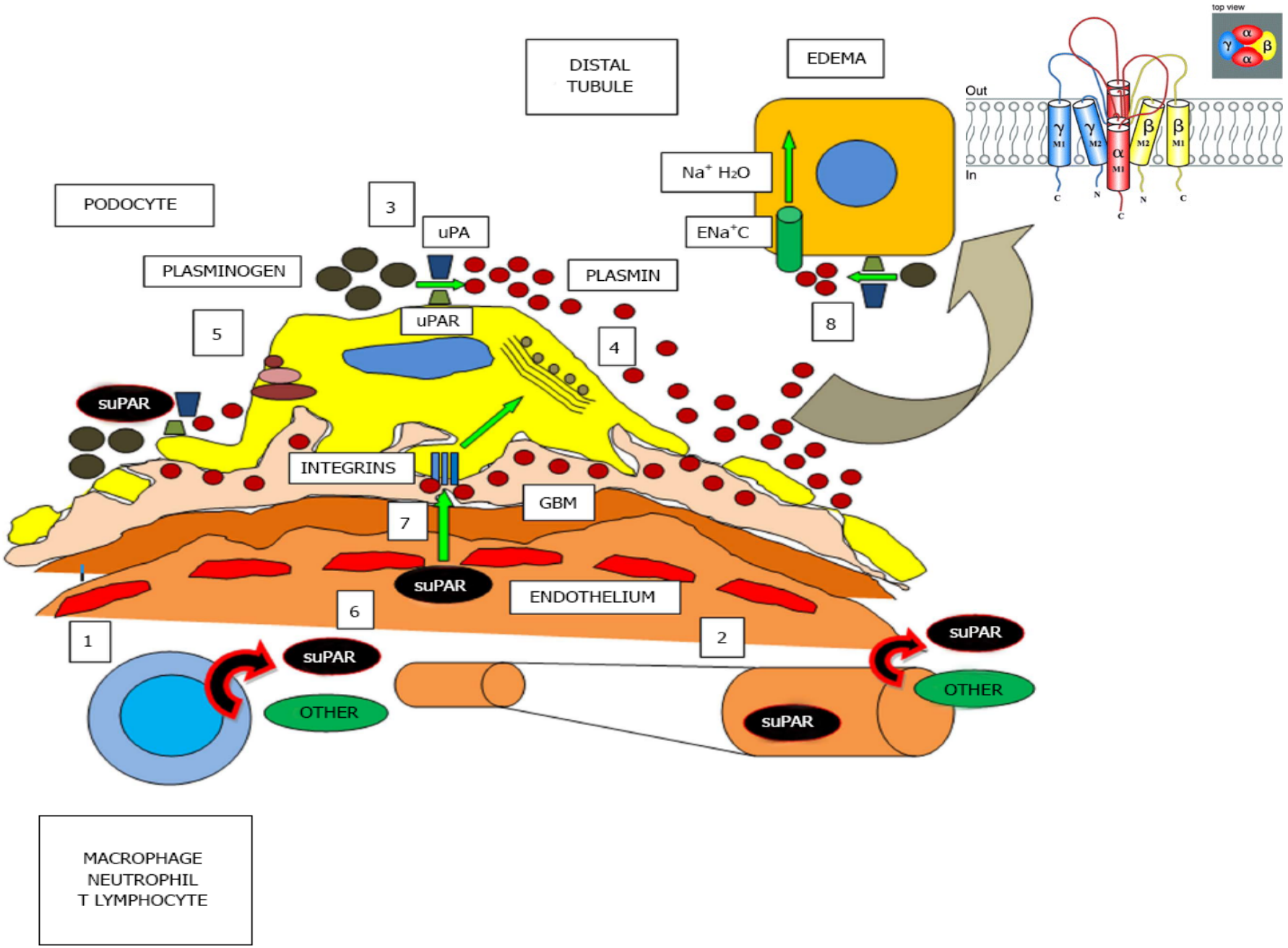
Warnock, D. G. *et al. Nat. Rev. Nephrol. 2014; 10: 146–157*

A novel model for stimulation of sodium reabsorption in nephrotic syndrome

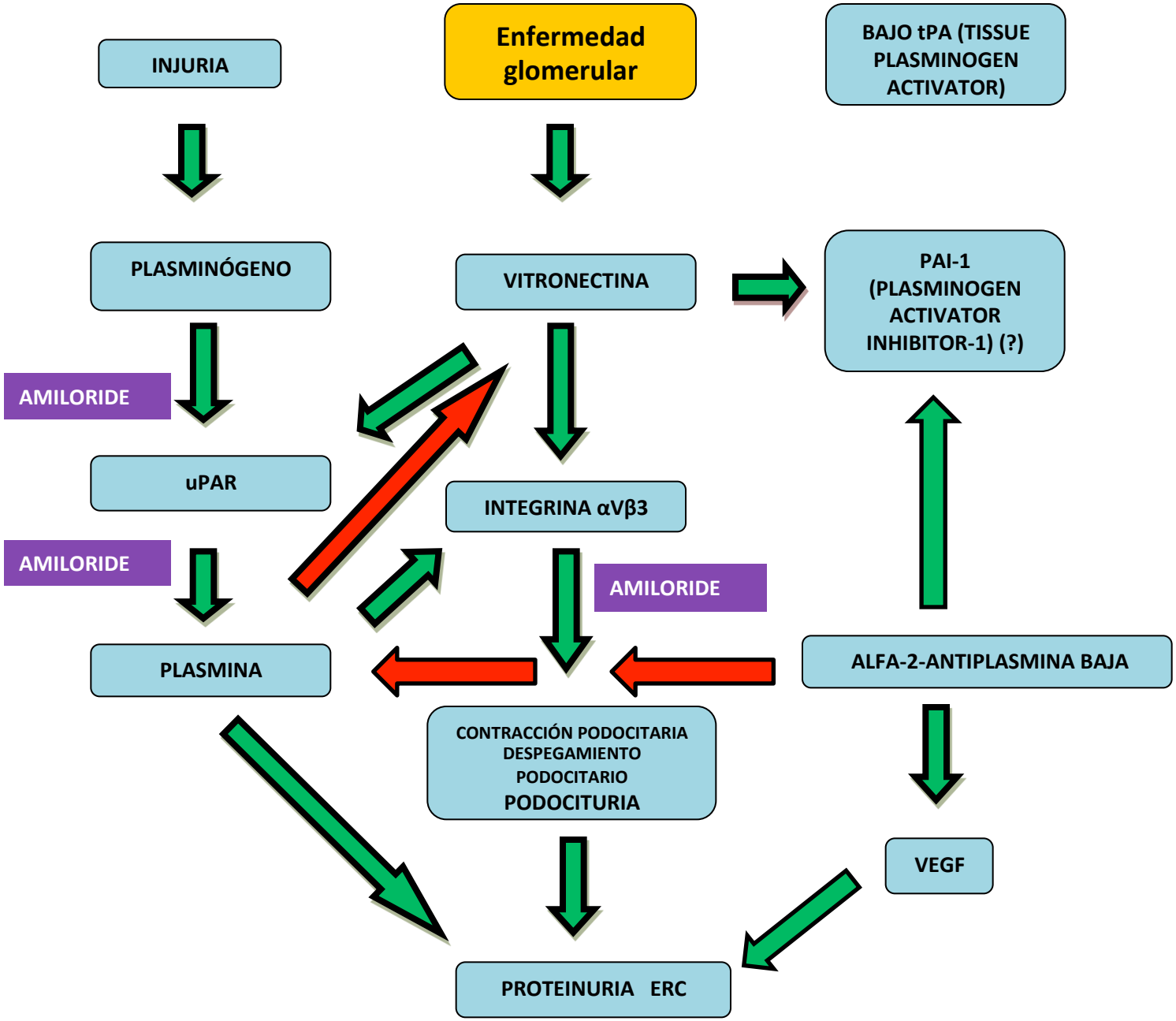


Relevant for human pathophysiology?

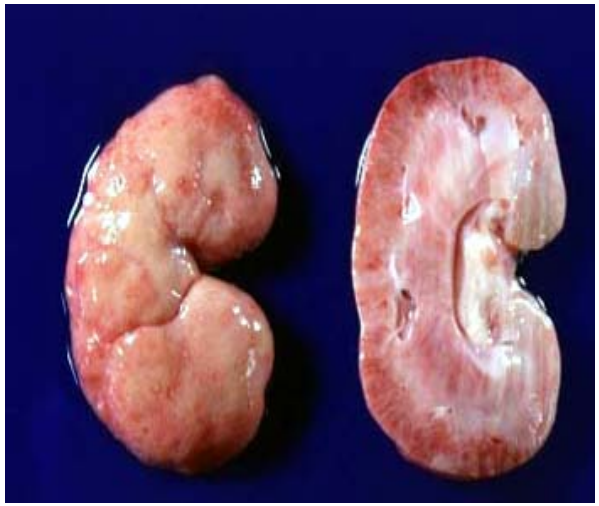
Trimarchi H. Focal segmental glomerulosclerosis and suPAR



World J Nephrol 2013 November 6; 2(4): 103-110



In press Case Reports in Nephrology



Have we fallen off target with concerns surrounding dual RAAS blockade?

Michael R. Lattanzio[1] and Matthew R. Weir[1]

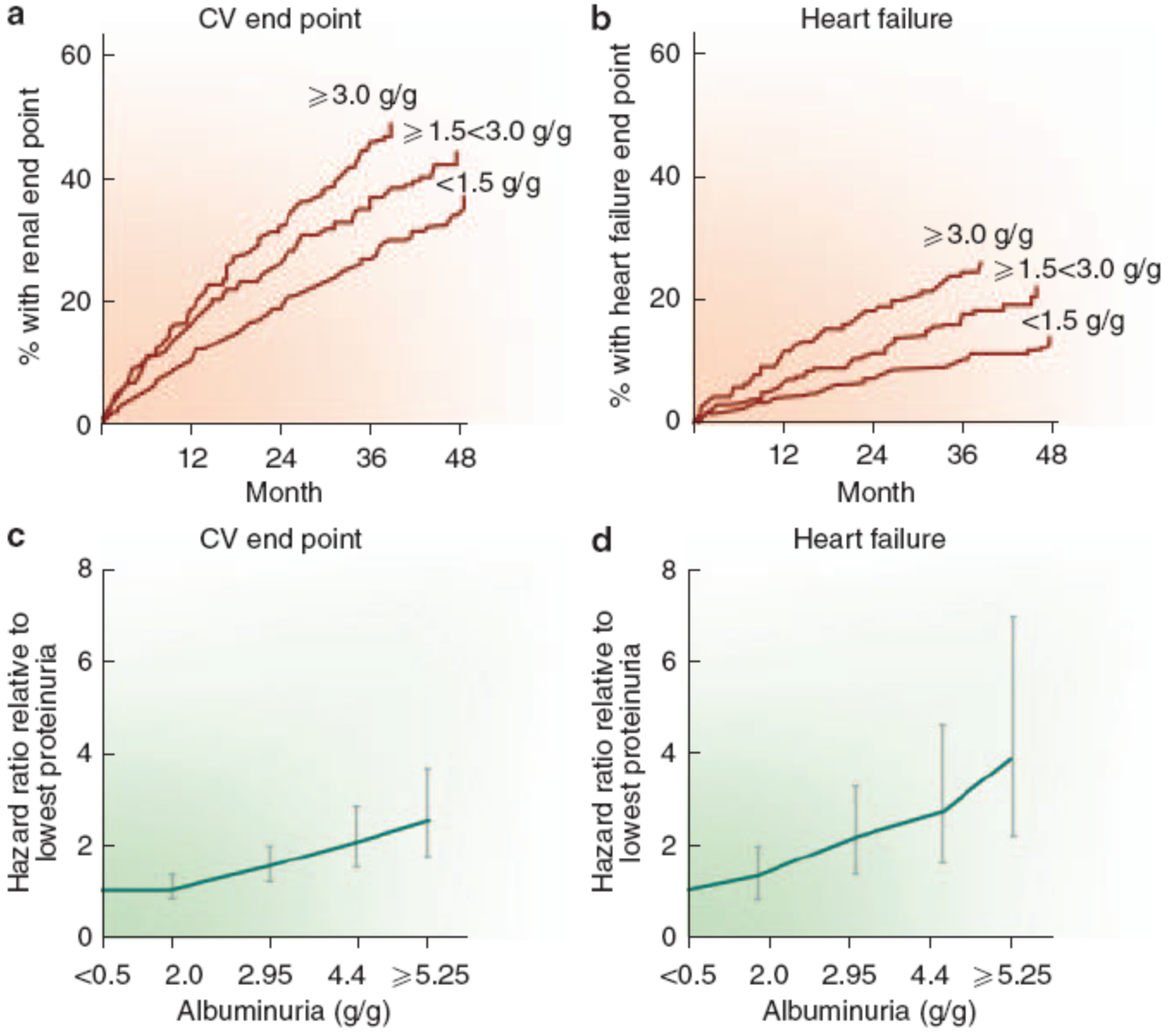
[1]*Division of Nephrology, Department of Medicine, University of Maryland School of Medicine, Baltimore, Maryland, USA*

Kidney International (2010) **78,** 539–545

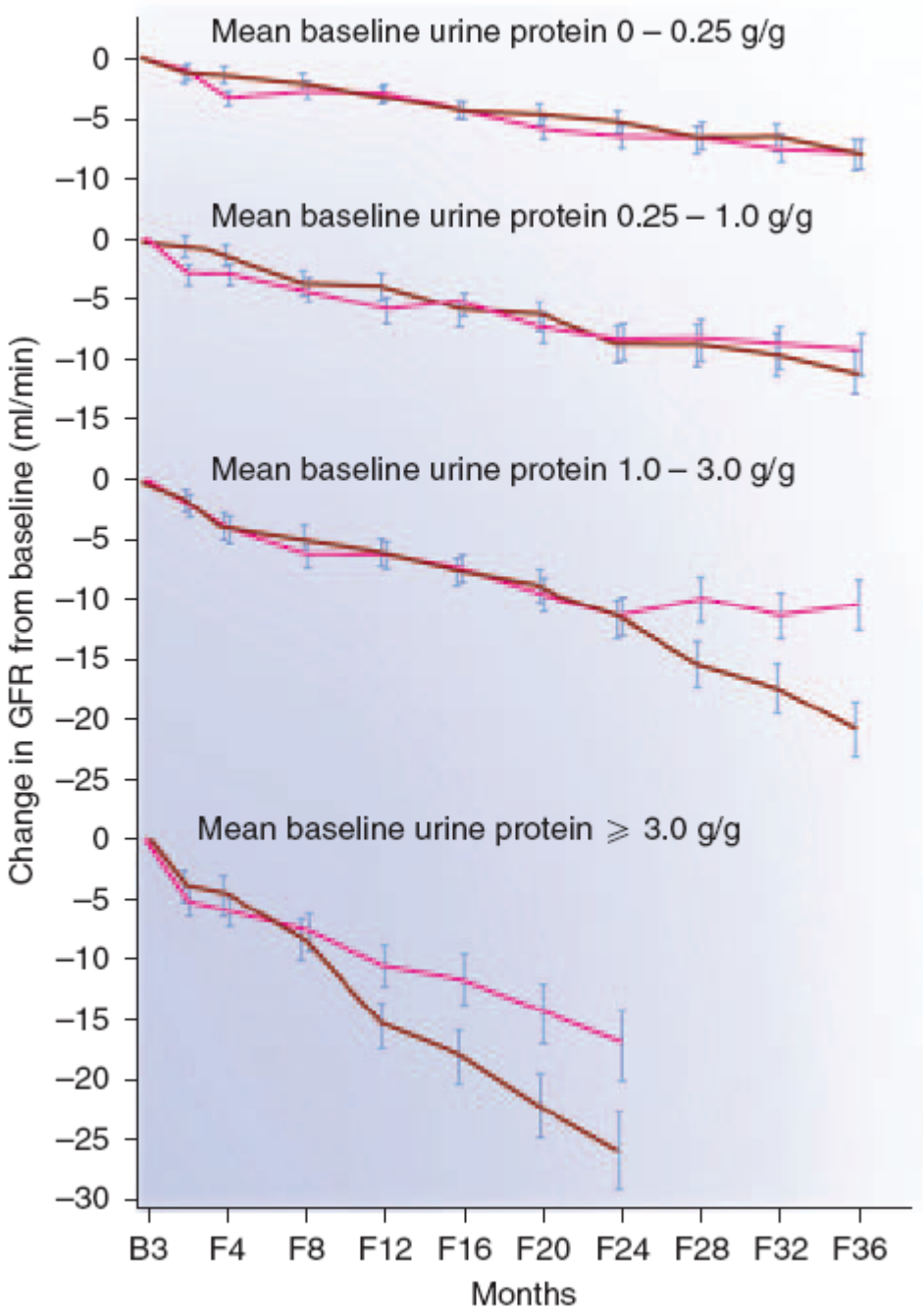
Dual RAAS blockade is desirable in kidney disease: Con

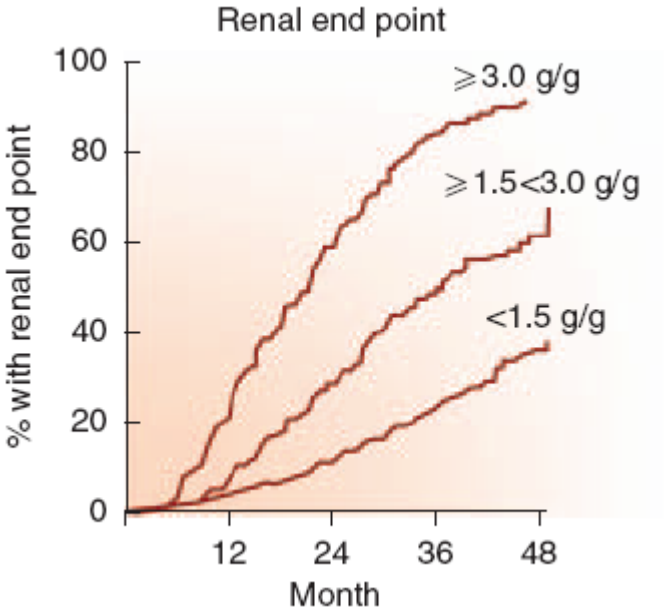
George L. Bakris[1]

Kidney International (2010) **78,** 546–549

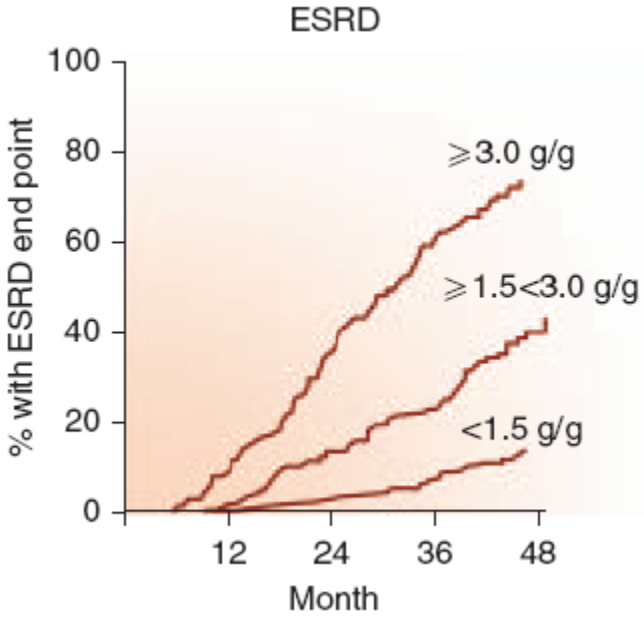

a
CV end point
% with renal end point
60
40
20
0
⩾3.0 g/g
⩾1.5<3.0 g/g
<1.5 g/g
12
24
36
48
Month
b
Heart failure
% with heart failure end point
60
40
20
0
⩾3.0 g/g
⩾1.5<3.0 g/g
<1.5 g/g
12
24
36
48
Month
c
CV end point
Hazard ratio relative to lowest proteinuria
8
6
4
2
0
<0.5
2.0
2.95
4.4
⩾5.25
Albuminuria (g/g)
d
Heart failure
Hazard ratio relative to lowest proteinuria
8
6
4
2
0
<0.5
2.0
2.95
4.4
⩾5.25
Albuminuria (g/g)

type 2 diabetic nephropathy





(doubling serum creatinine, ESRD, and/or death)



Kidney International (2010) **78,** 539–545

Pediatr Nephrol (2009) 24:1165–1172
DOI 10.1007/s00467-008-1110-9

ORIGINAL ARTICLE

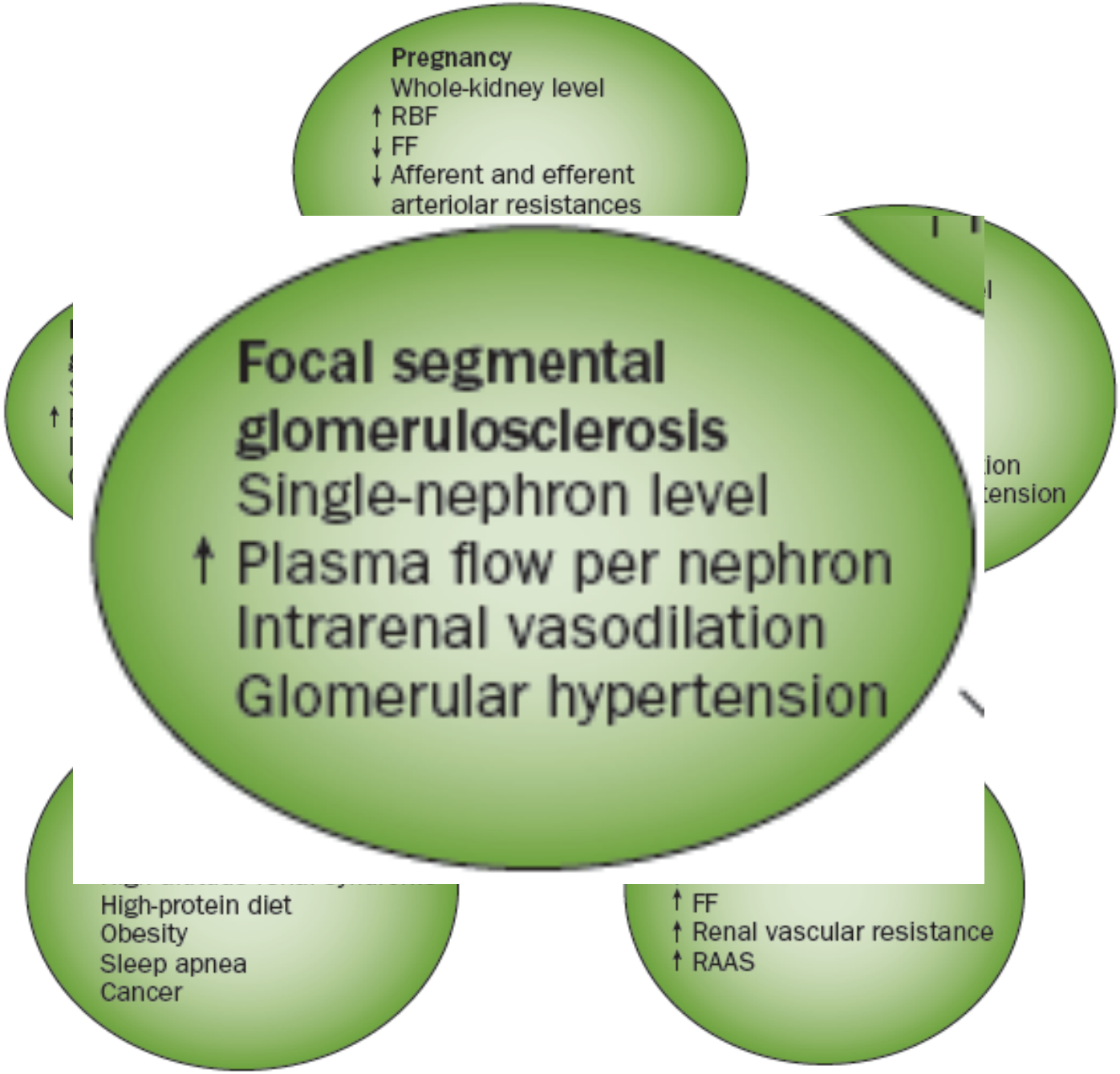
Circadian rhythms of diuresis, proteinuria and natriuresis in children with chronic glomerular disease

Amira Peco-Antić · Jelena Marinković · Divna Kruščić · Dusan Paripović

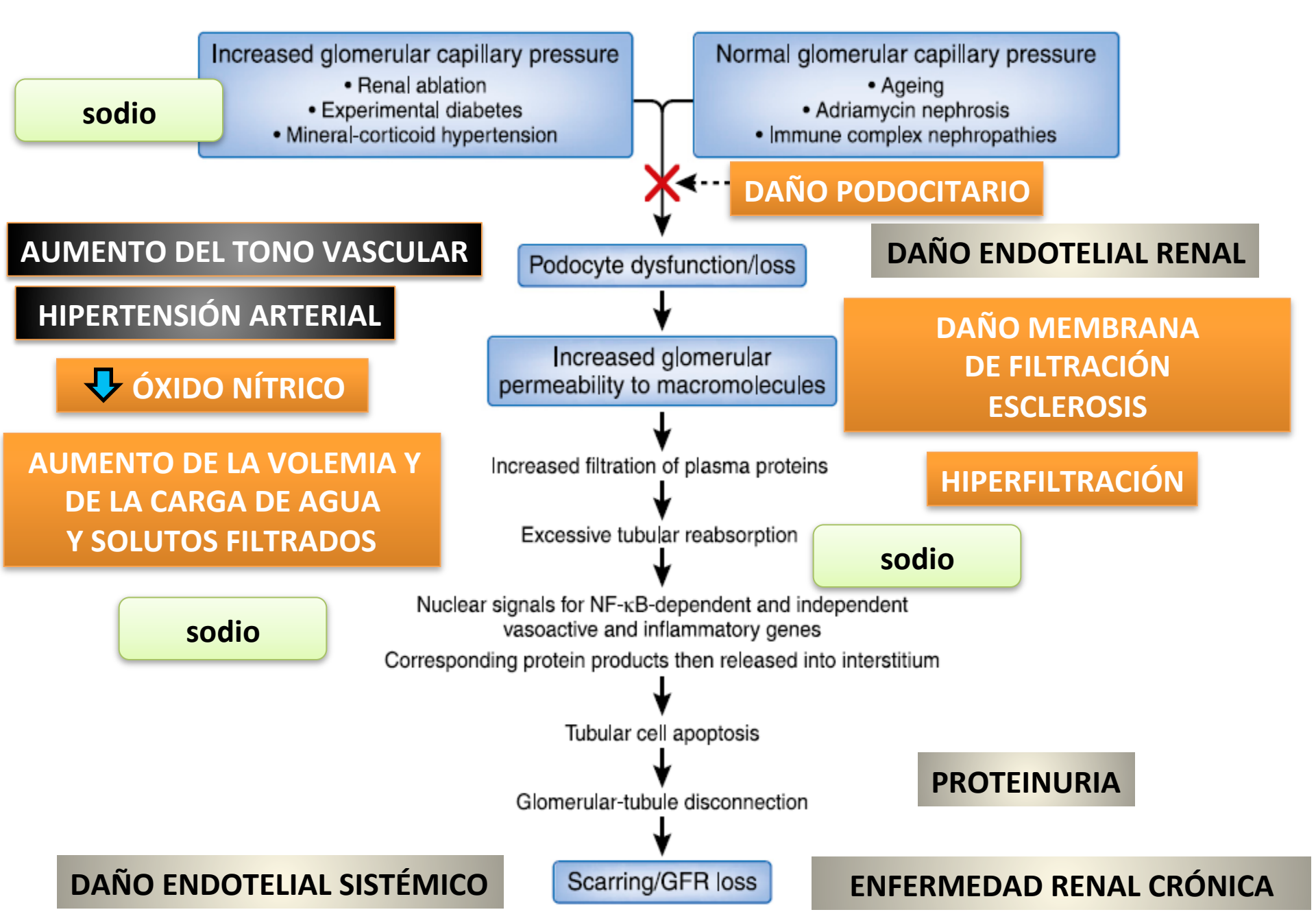
La caída nocturna en el Clearance de creatinina (TFG), diuresis, proteinuria y natriuresis era menor en sujetos con ERC estadío 3 vs ERC estadío 1-2

La presión arterial media (PAM) nocturna, así como los cocientes noche/día de la PAM, diuresis, proteinuria y natriuresis estaban en correlación negativa con la función renal (TFG).

La variación de la función renal diurna y la PAM nocturna están relacionadas a una caída en la TFG.



Helal, I. et al. Nat. Rev. Nephrol. 2012; 8: 293–300



Ruggenenti P, Cravedi P, Remuzzi G J Am Soc Nephrol 2012; 23: 1917–1928

BASIC RESEARCH www.jasn.org

THE MISSING LINK

DAÑO ENDOTELIAL RENAL

DAÑO ENDOTELIAL SISTÉMICO

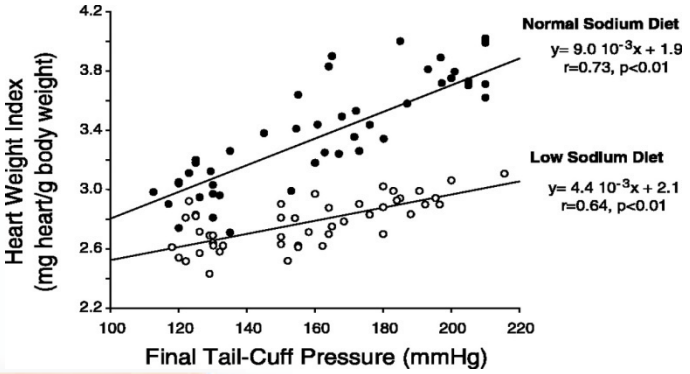
Loss of the Endothelial Glycocalyx Links Albuminuria and Vascular Dysfunction

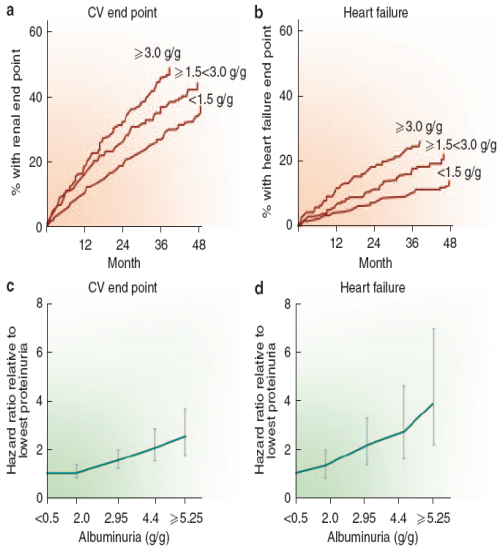
DAÑO PODOCITARIO

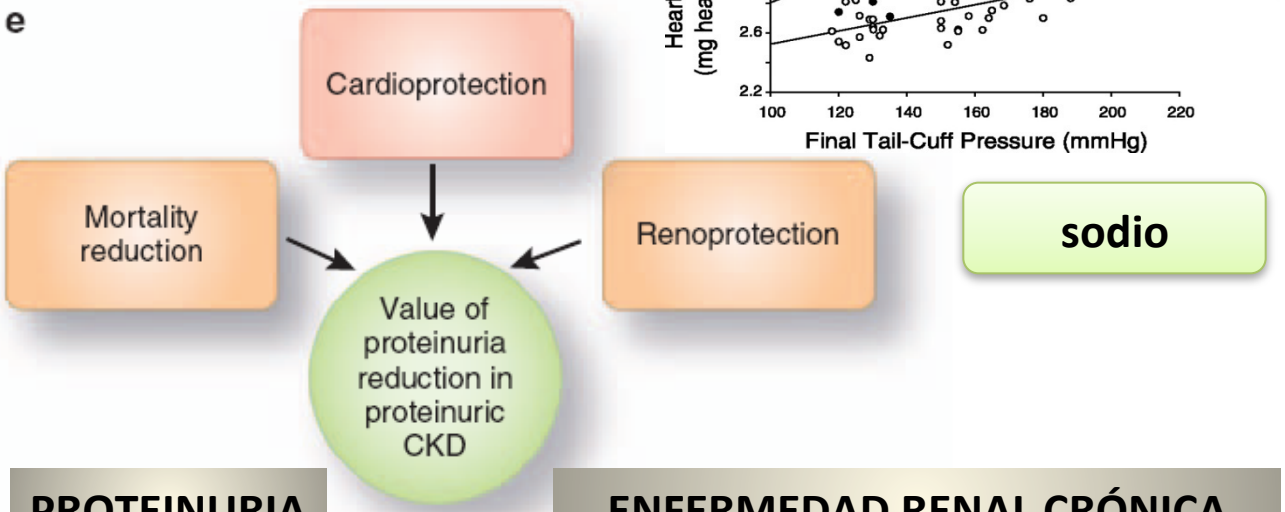
Andrew H.J. Salmon,*†‡ Joanne K. Ferguson,* James L. Burford,‡ Haykanush Gevorgyan,‡ Daisuke Nakano,‡§ Steven J. Harper,* David O. Bates,* and Janos Peti-Peterdi‡

DAÑO MEMBRANA DE FILTRACIÓN ESCLEROSIS

J Am Soc Nephrol 23: 1339–1350, 2012. doi: 10.1681/ASN.2012010017







sodio

PROTEINURIA

ENFERMEDAD RENAL CRÓNICA

Canal de Beagle, Tierra del Fuego Argentina