The Renal Medulla

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CRC Centre de Recherches Cordeliers

UPMC Sorbonne Universités

The Renal Medulla : Outline

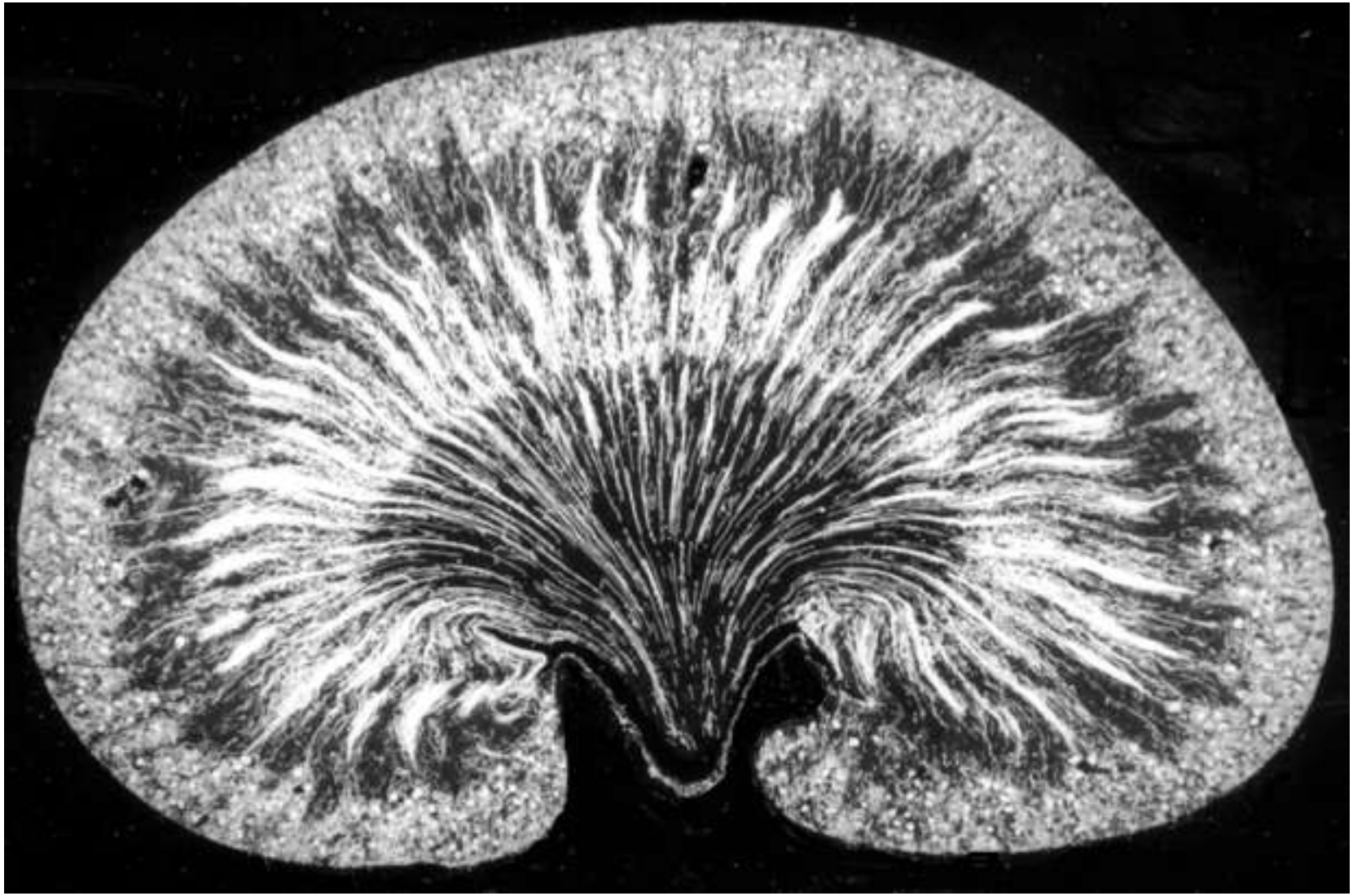
1. Anatomy / Vascularisation

2. Urine concentration

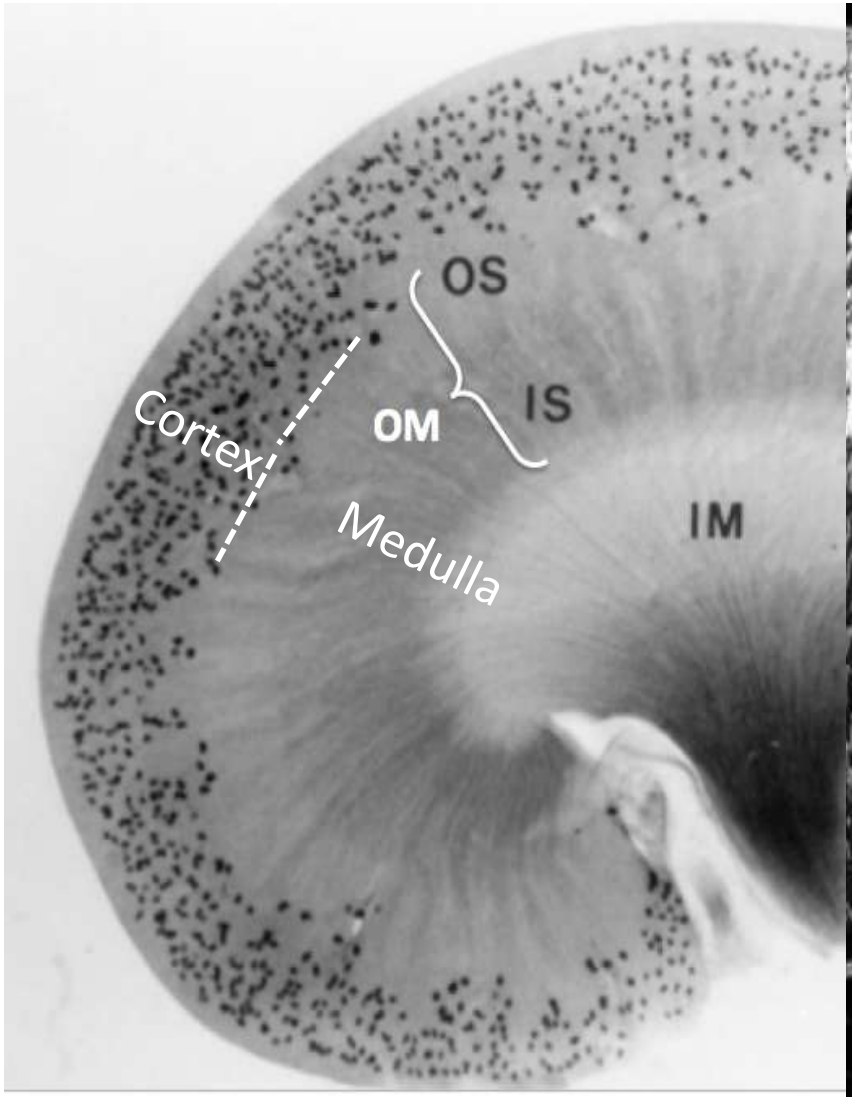
3. Axial heterogeneity of some segments

Vascularisation of the medulla and tubulo-vascular relationships

Rat kidney. Arterial filling with Microfil silicone rubber



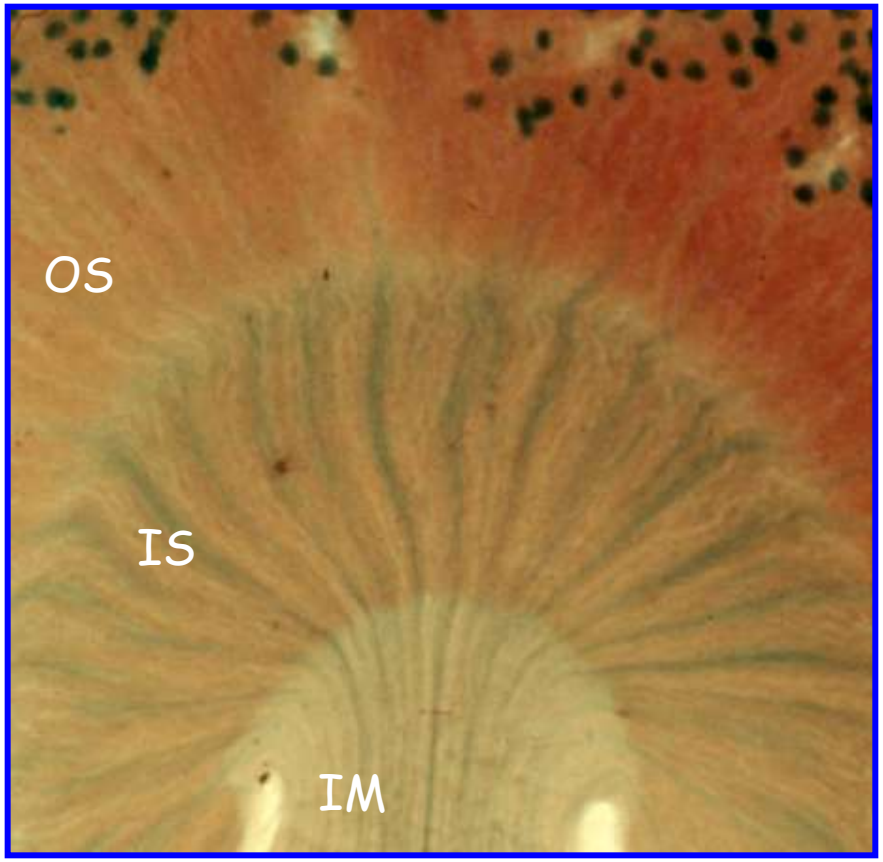
Alcian Blue staining



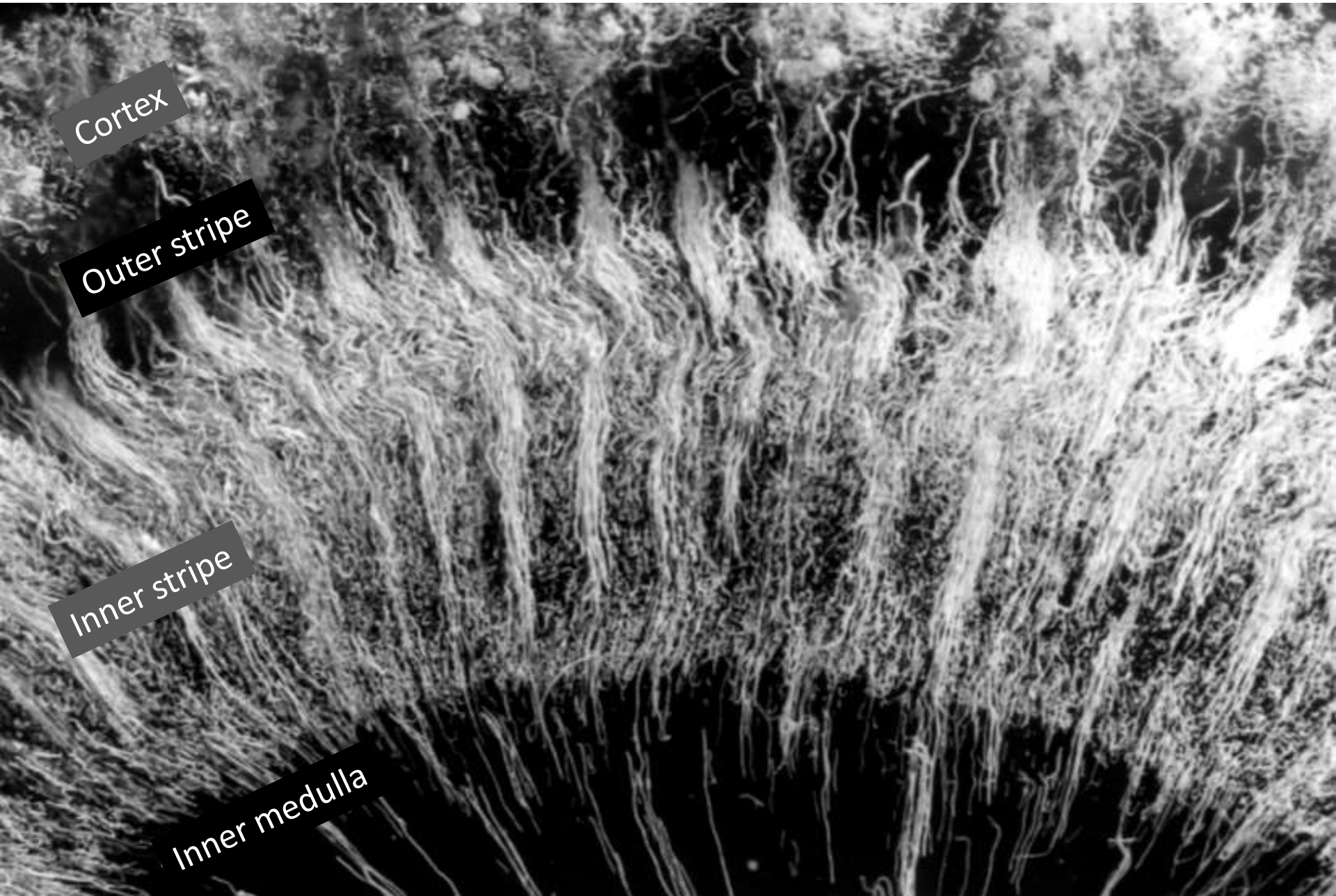
Filling of arterial vessels

Alcian Blue staining (dye infused in vivo, i.v.)

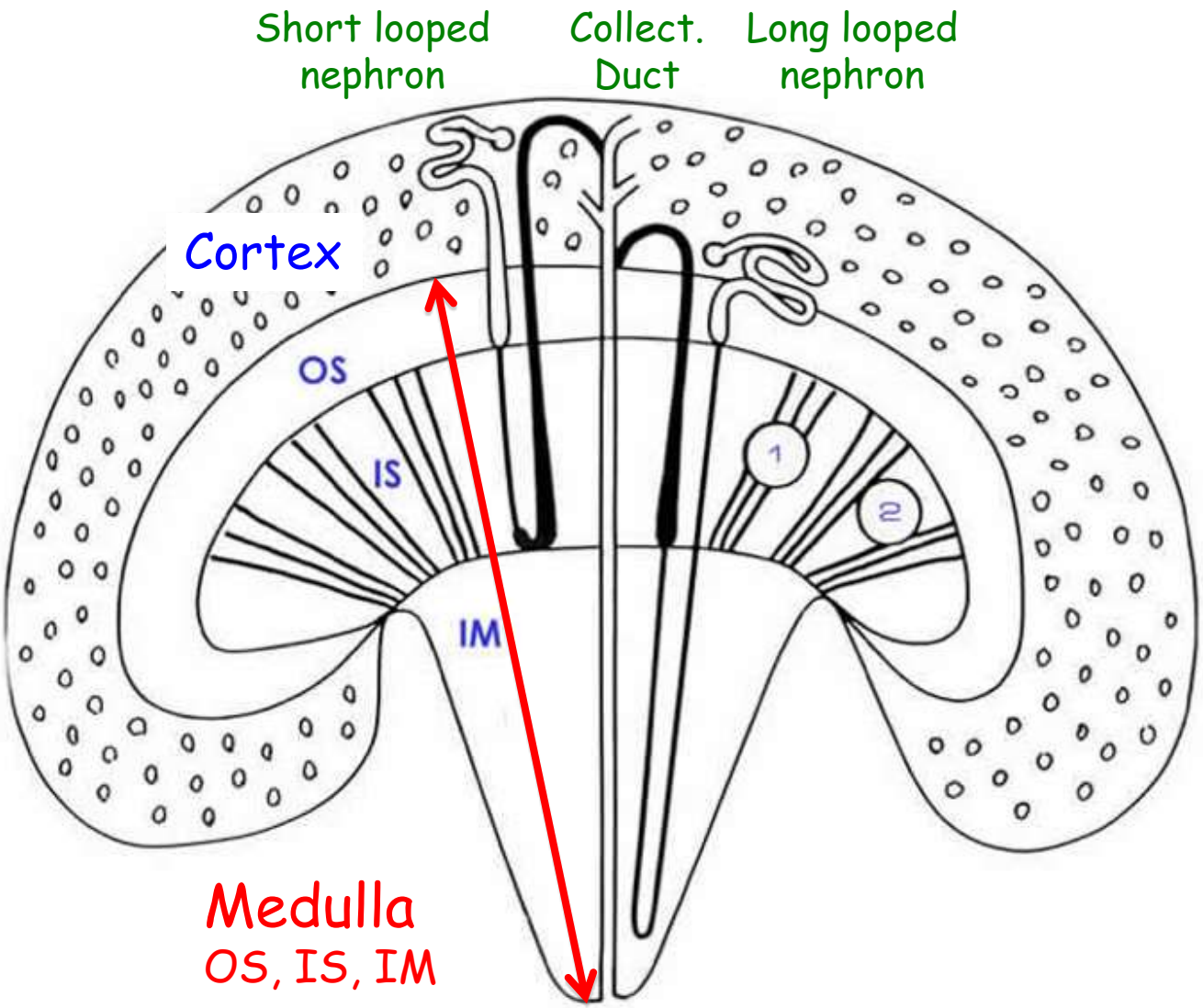
See the vascular bundles in the IS. They are highways to and from the IM



Outer medulla. ARTERIAL filling



Different zones of the mammalian kidney



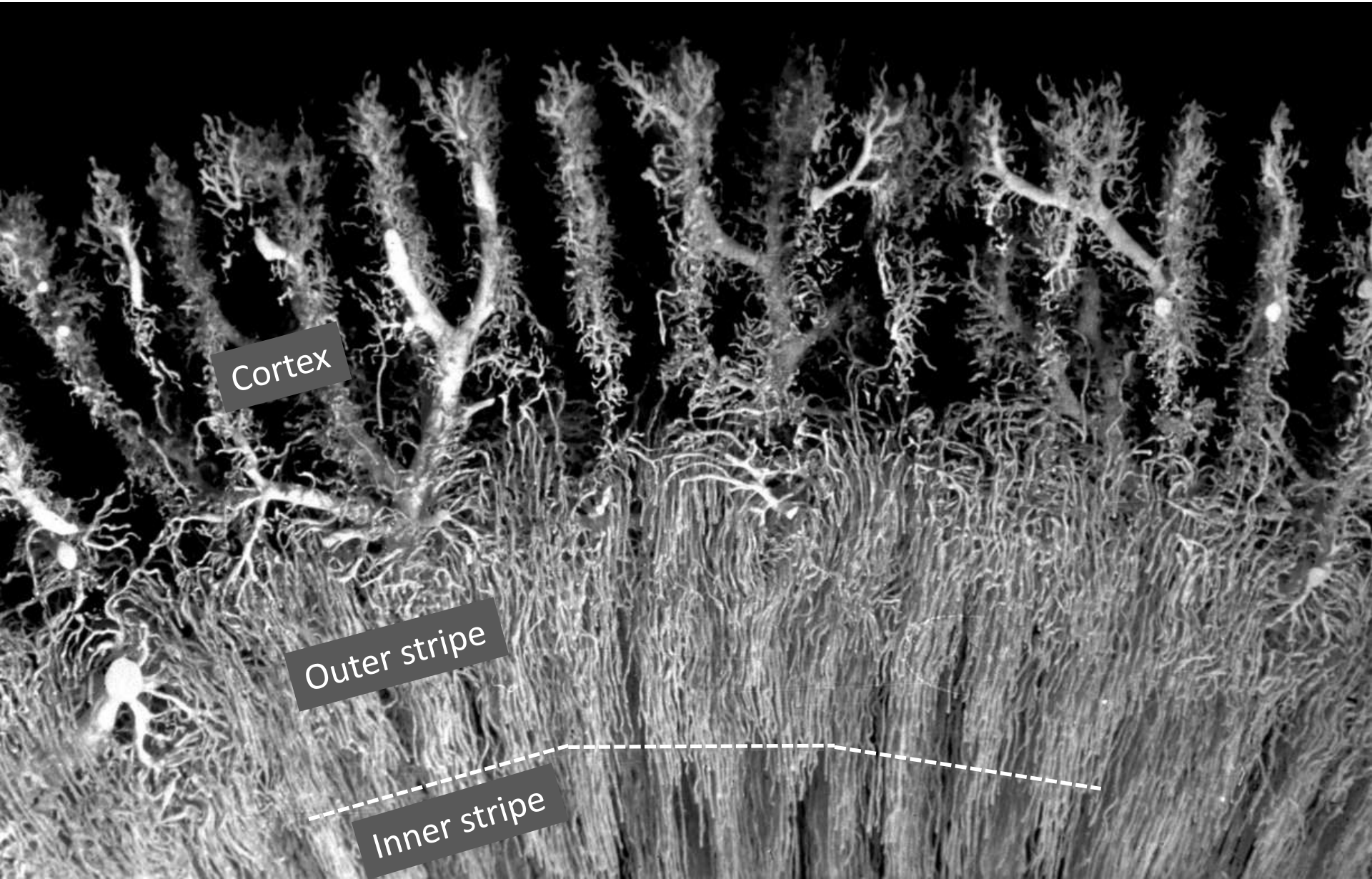
VASCULARISATION

in IS, alternance of

①	②
Vascular bundles	Dense interbundle capillary plexus around tubules (MTAL)
↓↑	
to and from IM	

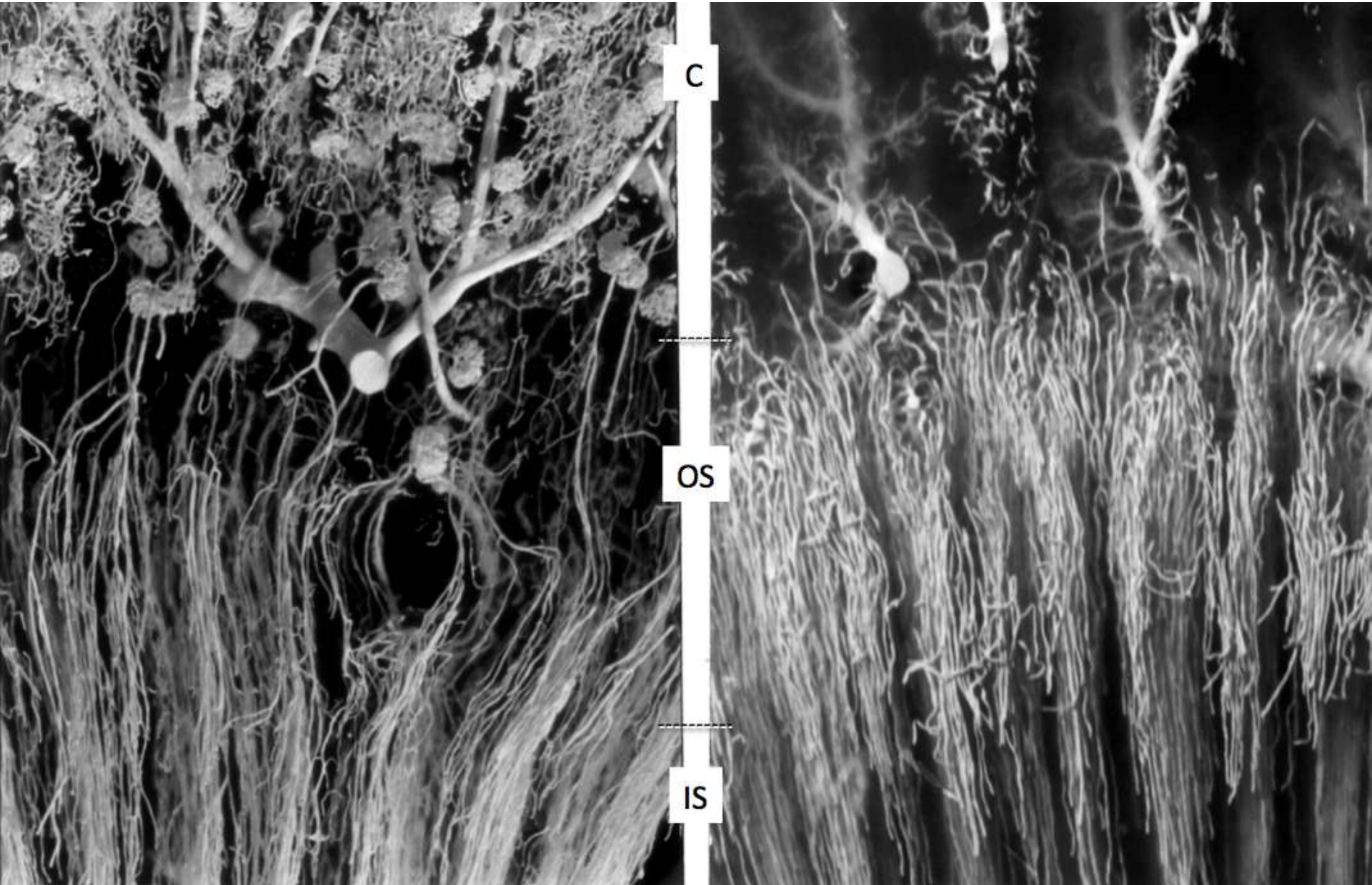
in IM
parallel vasa recta
with few capillaries

Cortex and outer medulla. VENOUS filling

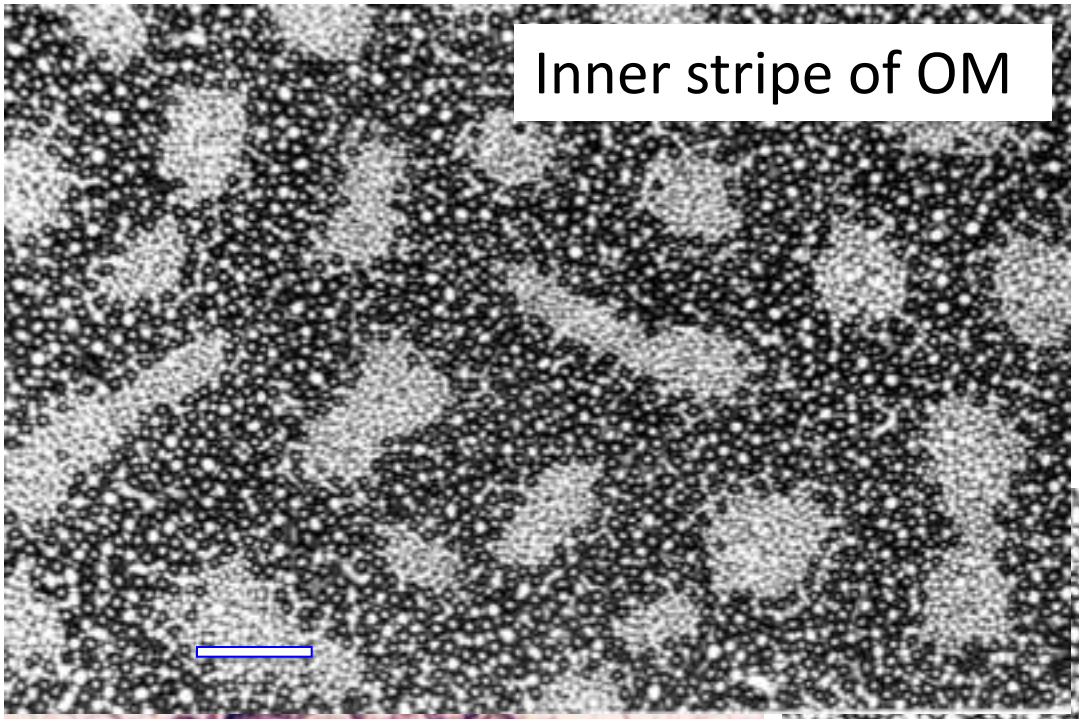


Deep cortex and outer stripe of outer medulla

ARTERIAL filling VENOUS filling

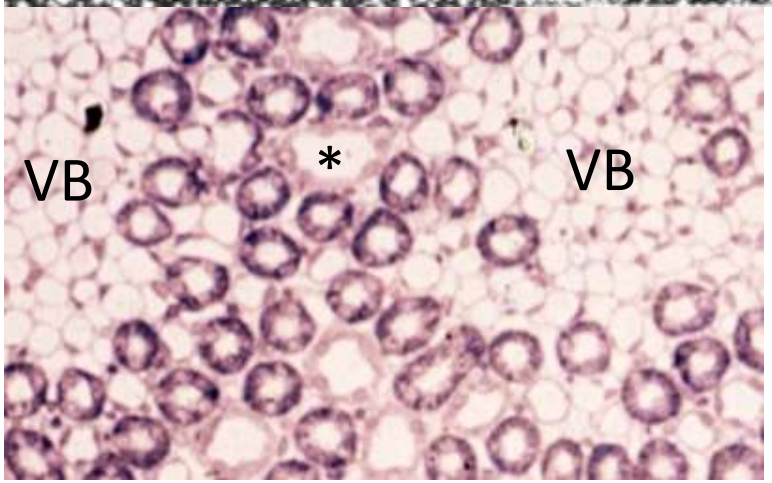


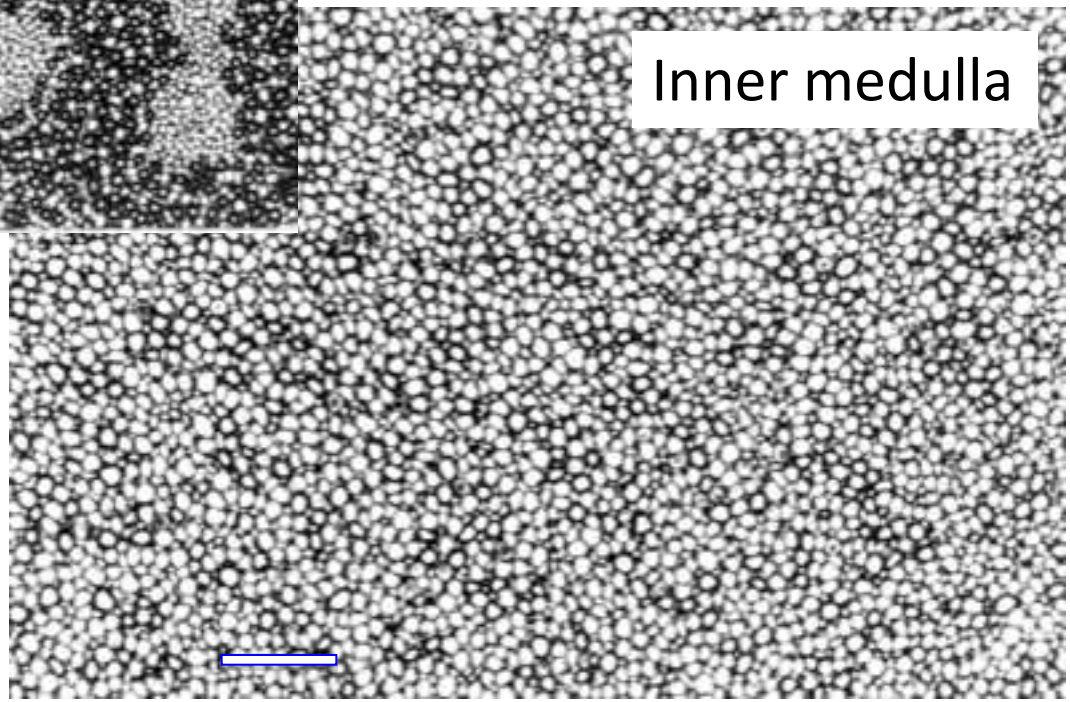
Cross sections through the medulla



Strong compartmentation between:

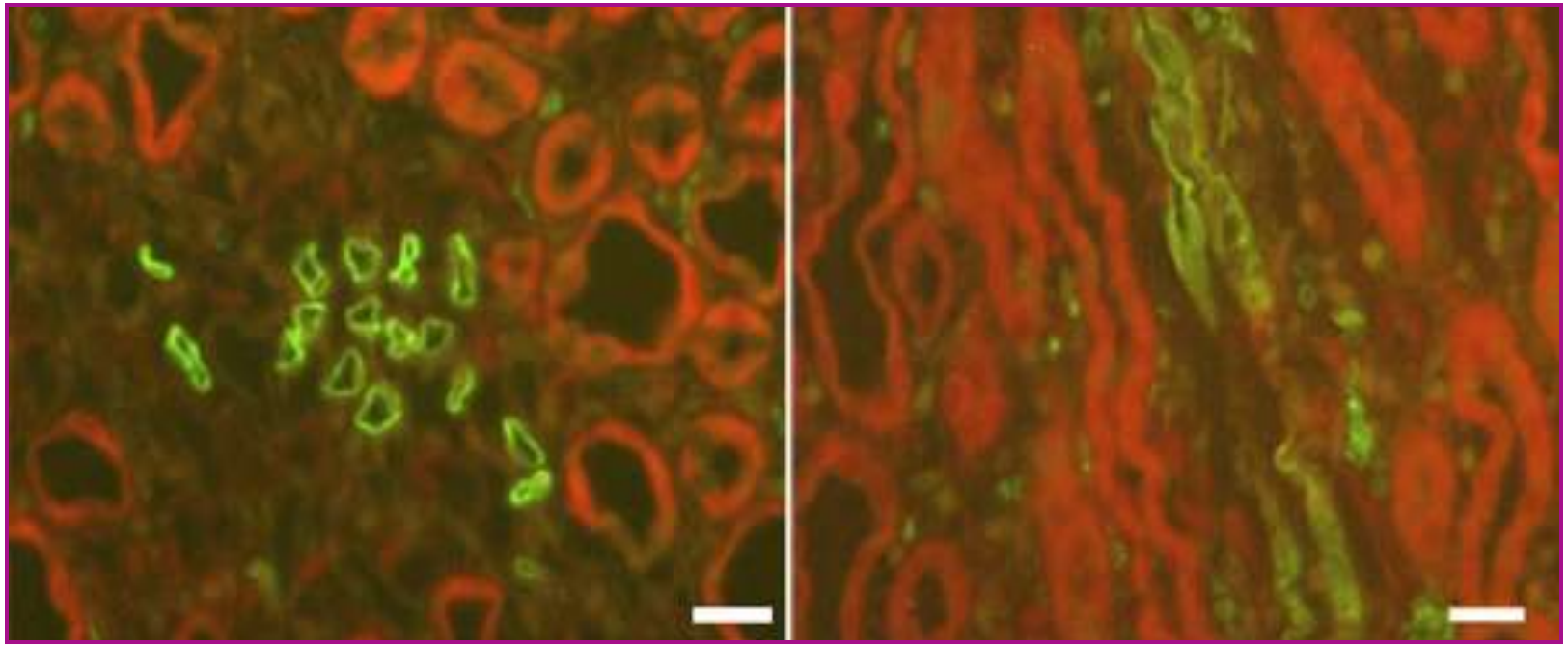
- Vascular bundles (VB)
- Interbundle regions





Immunolocalization of UT-B in vascular bundles (rat kidney inner stripe)

Cross section | Longitudinal section

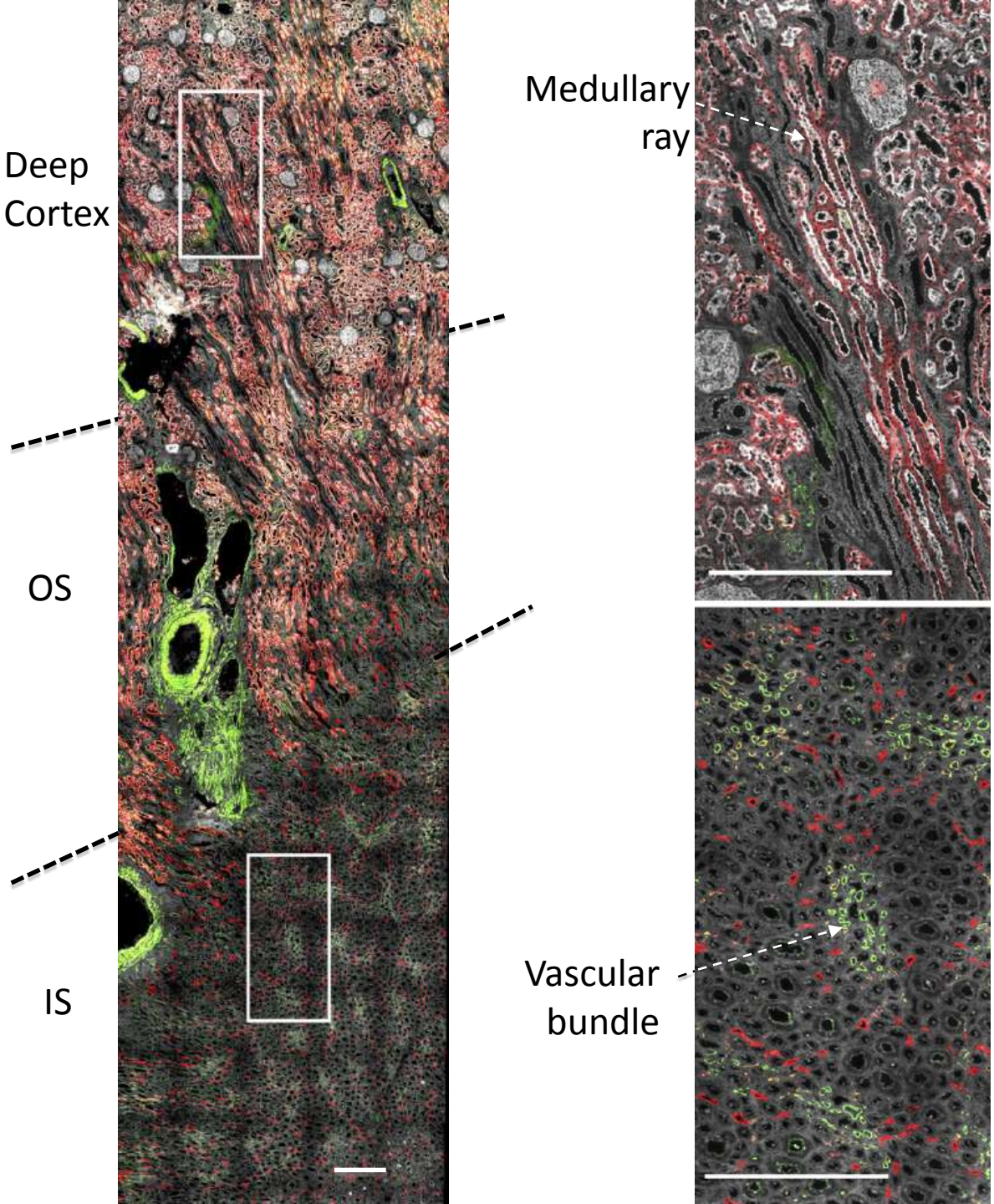


Arterial vasa recta endothelium and red blood cells are labelled

From Hu, Bankir, and Trinh-Trang-Tan, Kidney Int. 2000

Architecture of the human renal medulla

Pannabecker's group
Am. J. Physiol.-Renal. 309: F627–F637, 2015



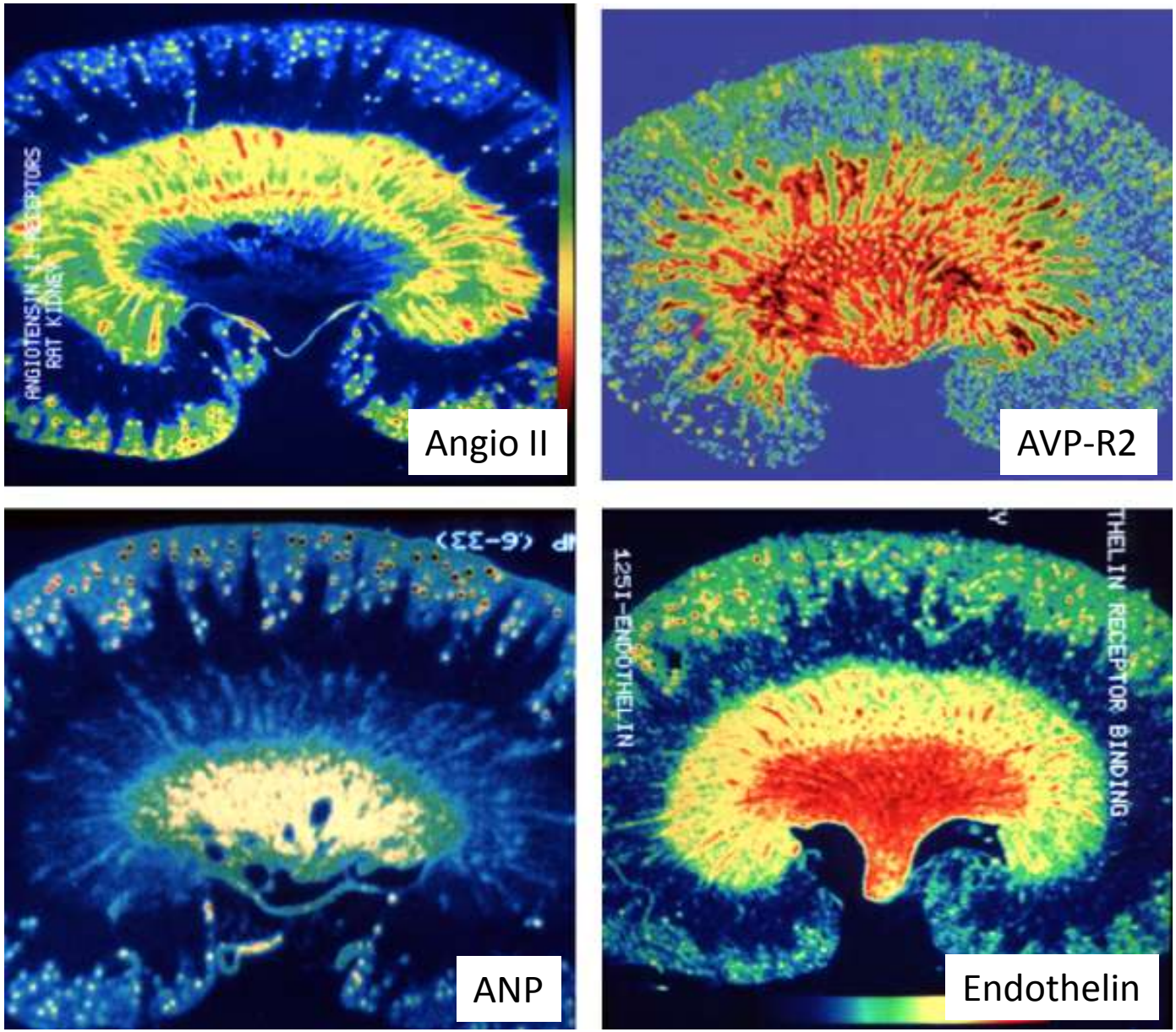
AQP1
descending thin limbs
descending vasa recta

UT-B
descending vasa recta

wheat germ agglutinin
nephrons, blood vessels
glomeruli

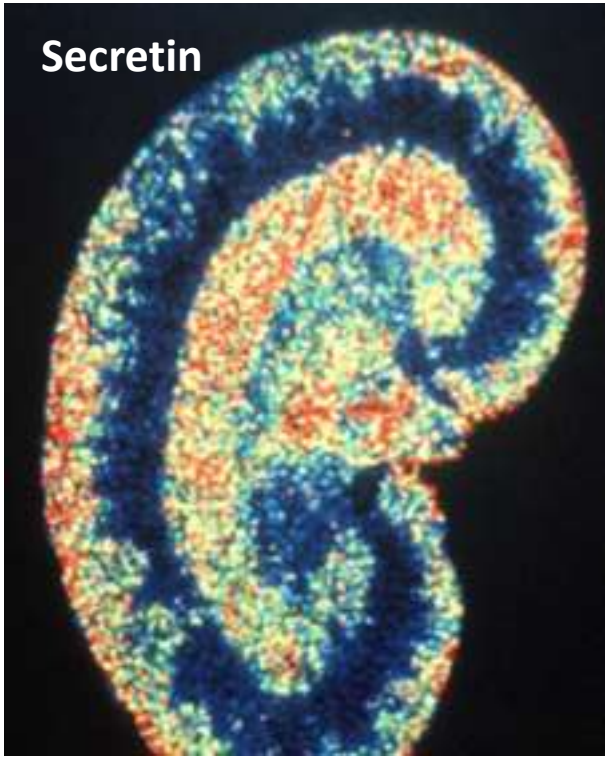
Scale bar = 500 µm

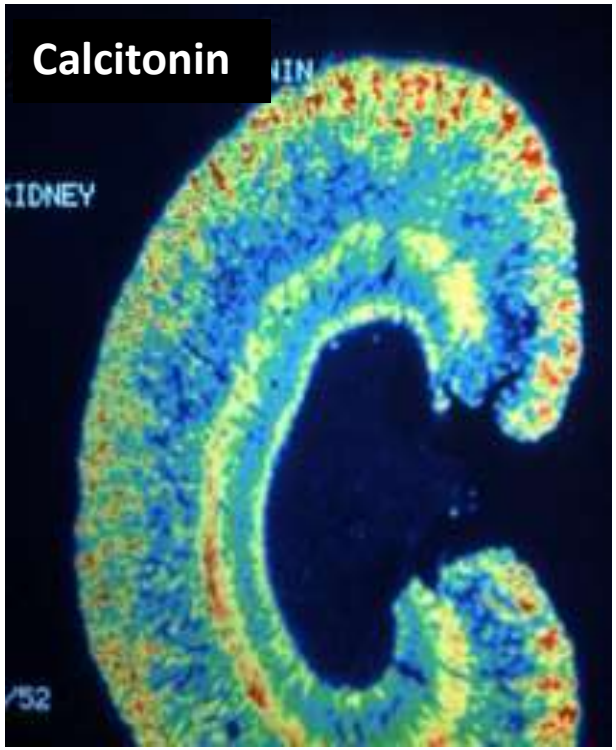
Autoradiograms of hormone binding to the rat kidney

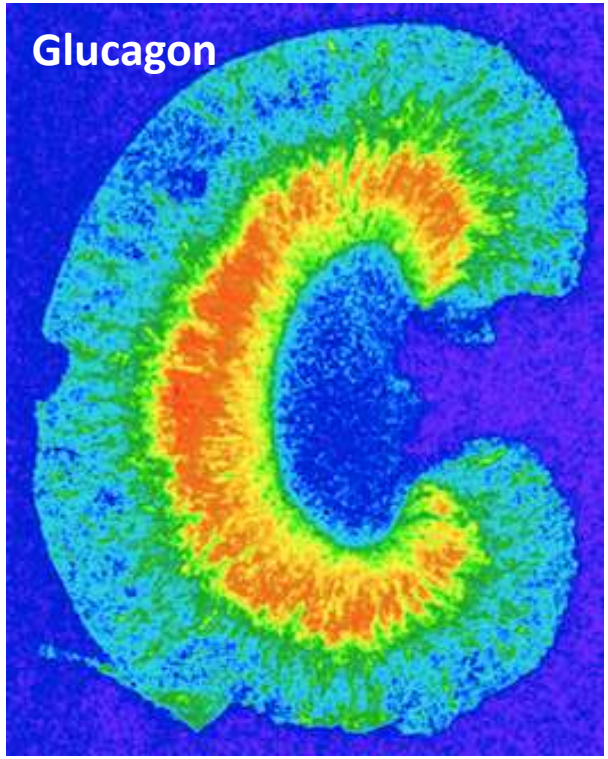


Autoradiograms by F. Mendelsohn (Australia) and Robert Speth (USA)

Autoradiograms of hormone binding to the rat kidney







Autoradiograms by F. Mendelsohn (Australia) and Robert Speth (USA)

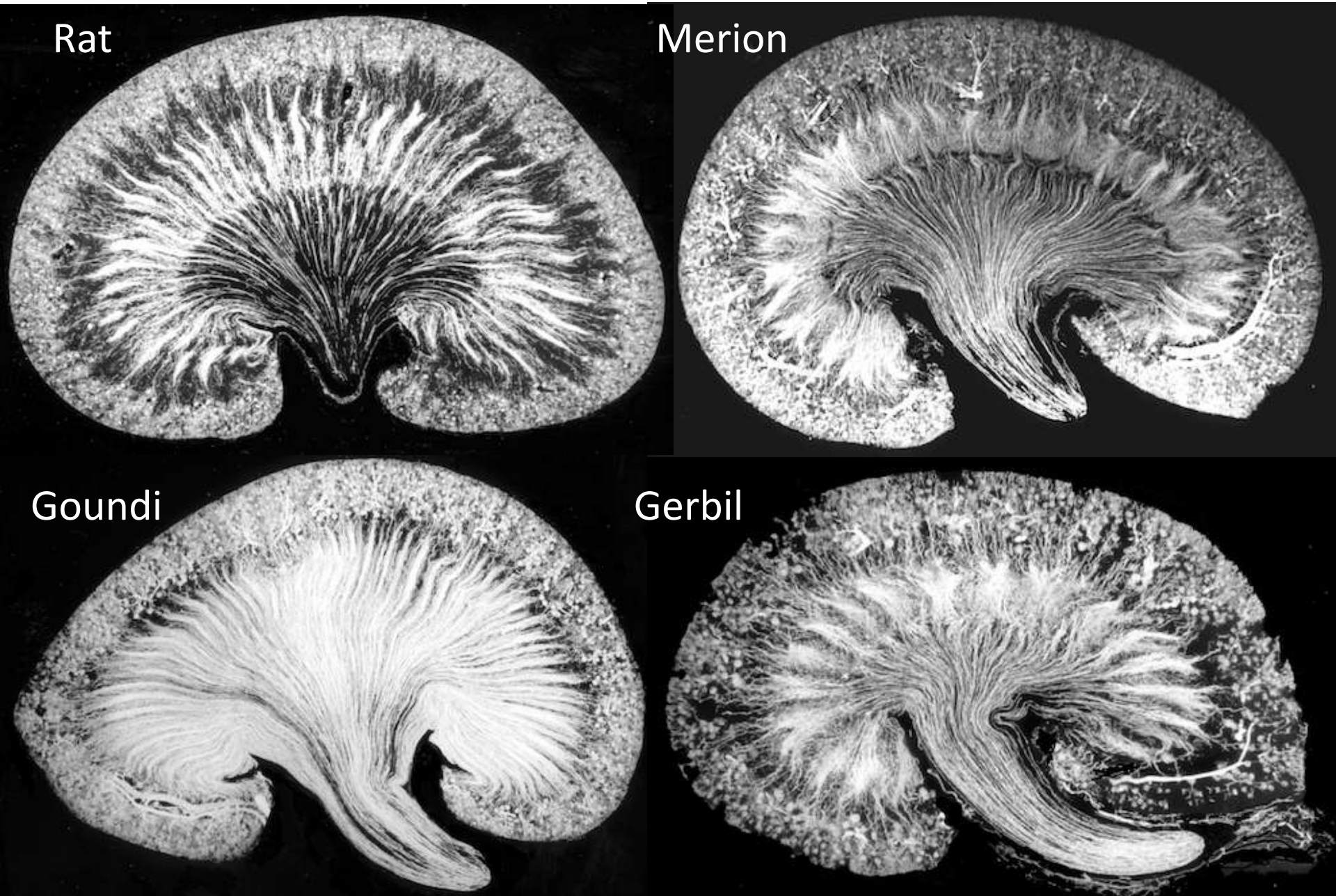
The Renal Medulla : Outline

1. Anatomy / Vascularisation

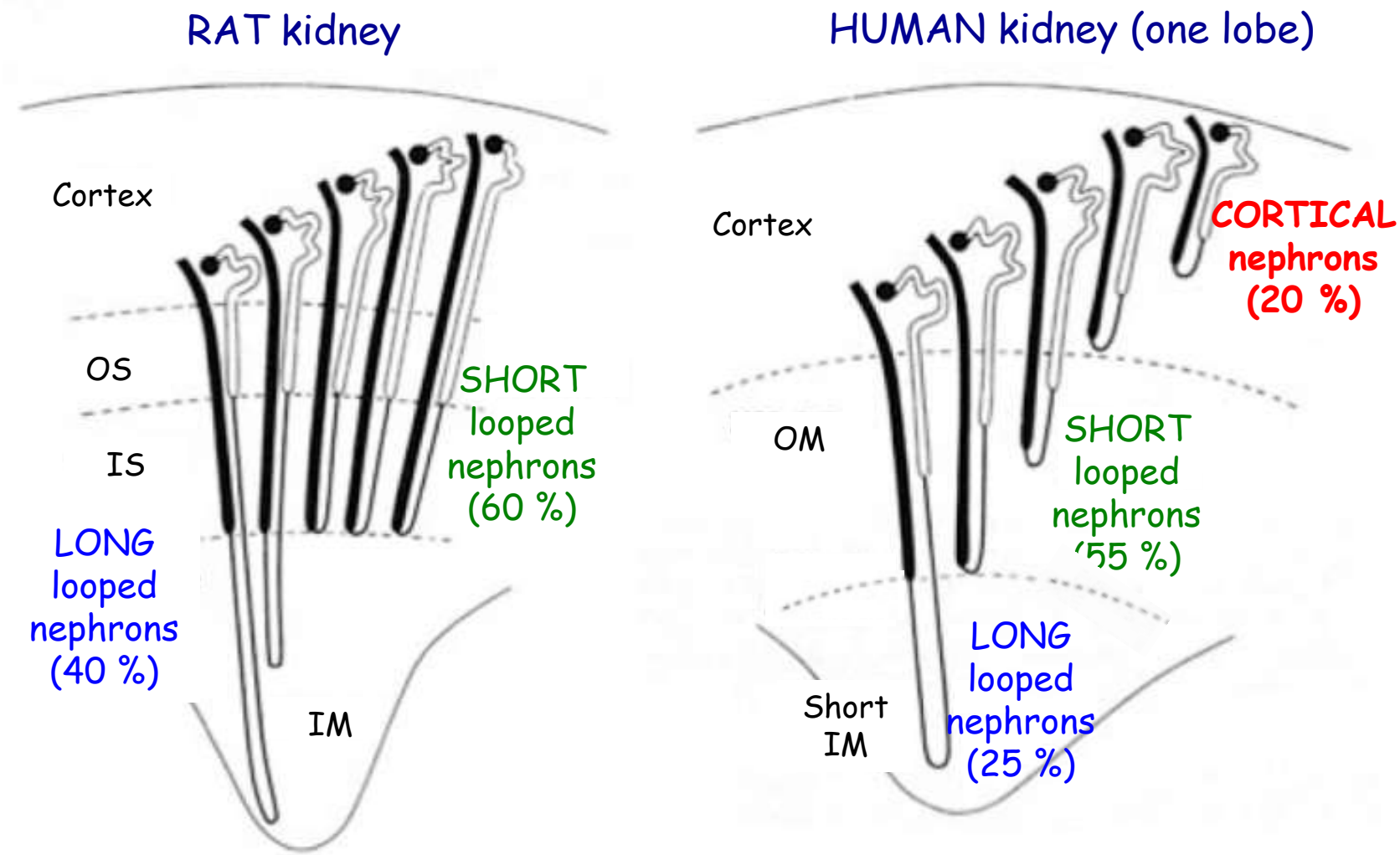
2. **Urine concentration**

3. Axial heterogeneity of some segments

Adaptation to better urine concentrating ability :
Not only medullary length but also structural adaptation of the IS



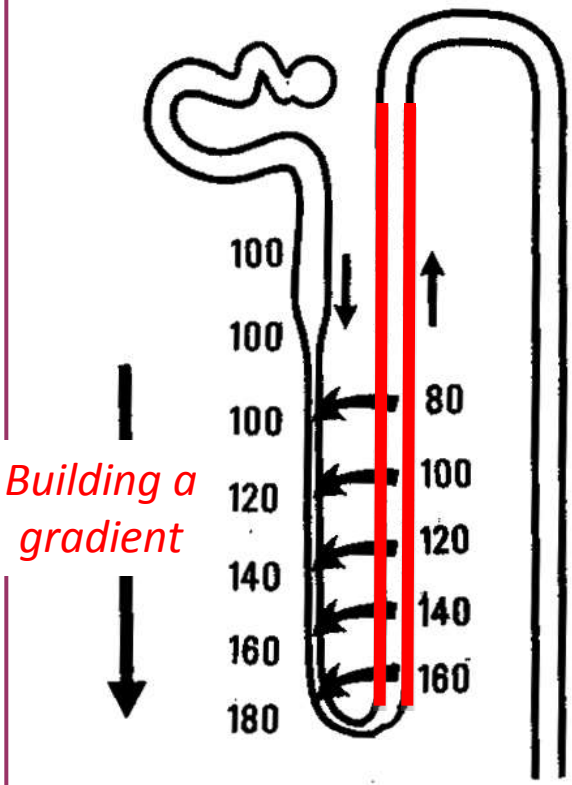
Nephron length



Counter-current exchange

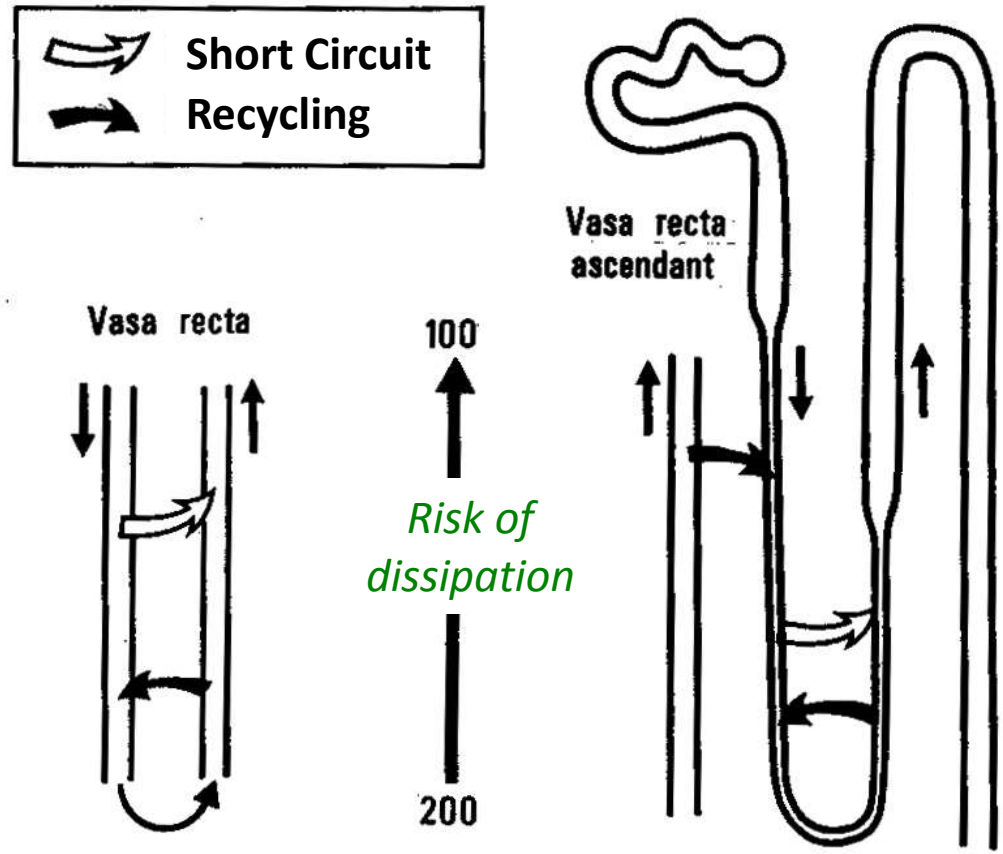
Counter-current multiplication

COUNTER-CURRENT MULTIPLICATION CREATES a concentration gradient



ACTIVE transport (example: Na reabsorption in TAL)

COUNTER-CURRENT EXCHANGE PREVENTS the DISSIPATION of a concentration gradient



PASSIVE diffusion between two parallel structures

Urea handling in the kidney

The kidney needs to excrete :

Not only **electrolytes** (Na, K, Ca, Phosphate, etc...)

But also the soluble end-products of **protein** metabolism

End products of the metabolism

Carbohydrates → CO_2 + H_2O (only)

Lipids → CO_2 + H_2O (only)

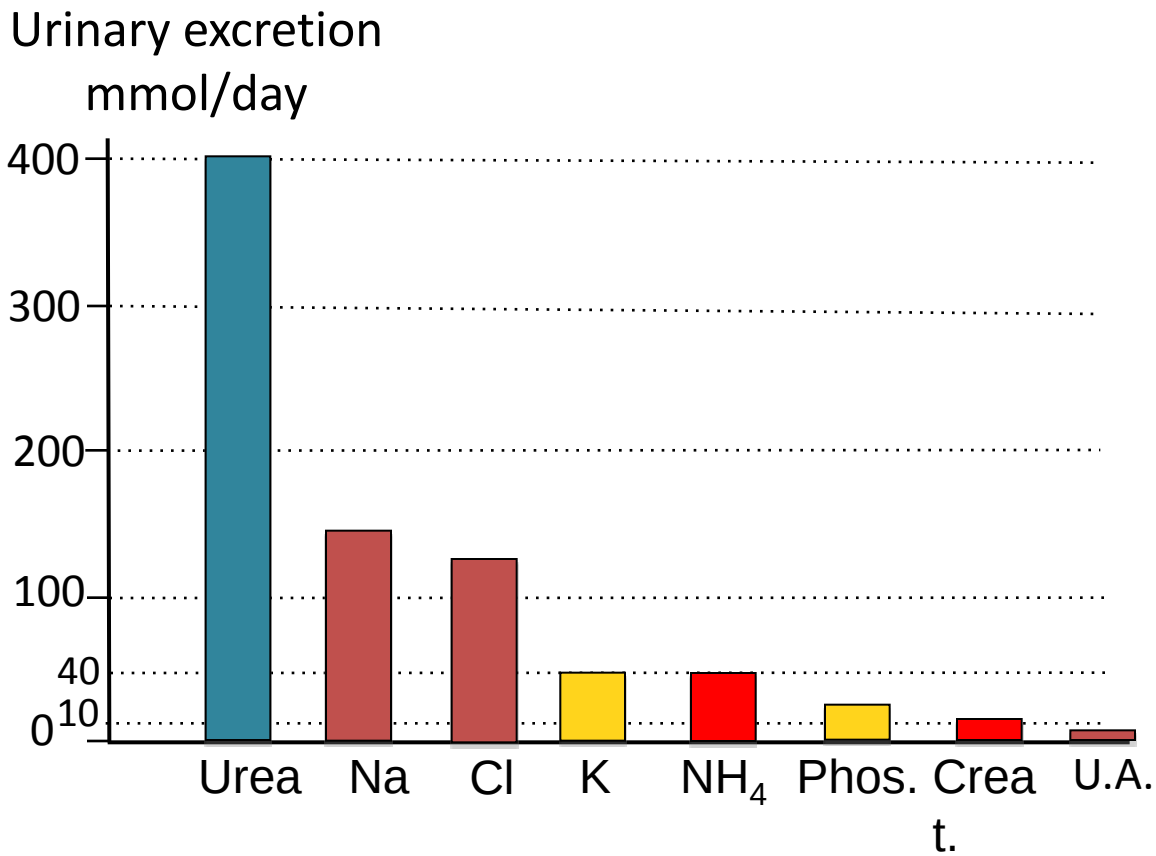
Proteins → CO_2 + H_2O

Urea, Ammonia, Uric acid, Creatinine PO_4, SO_4

Nitrogen
Strong acids

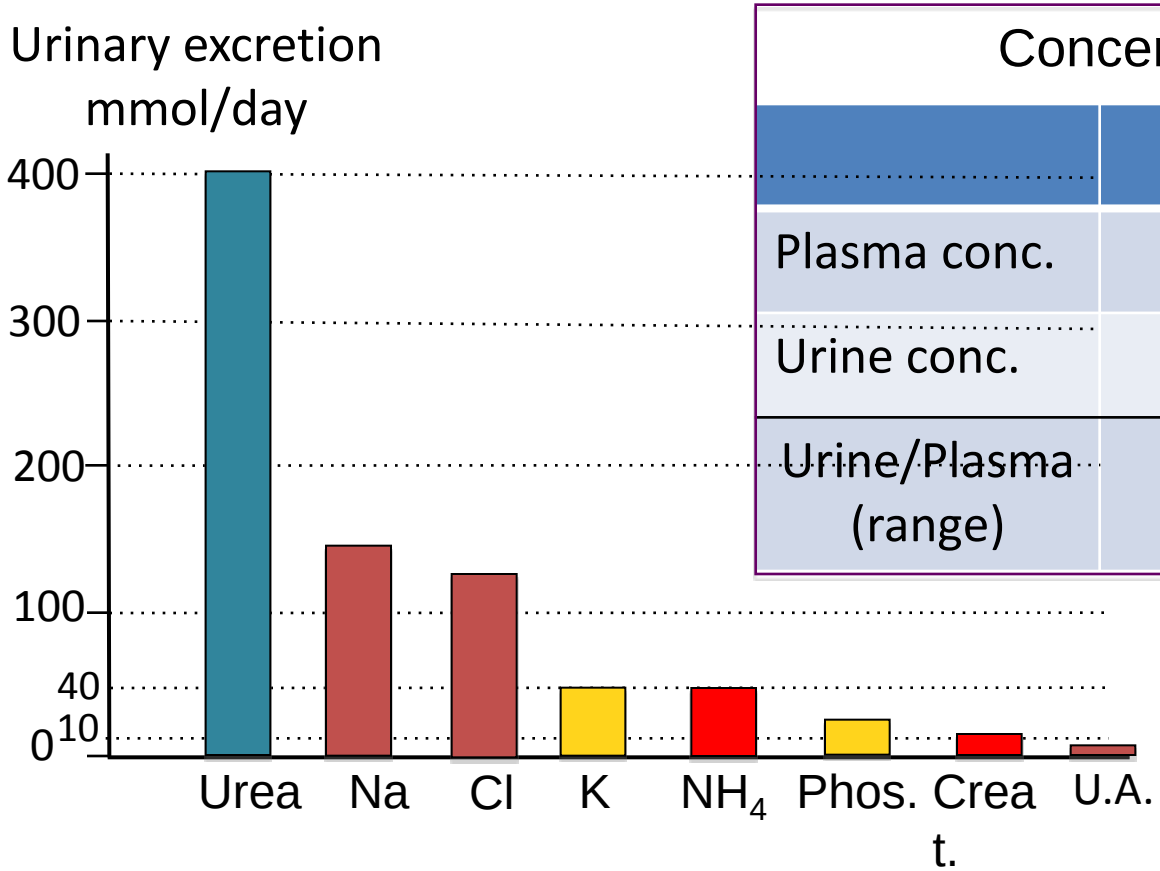
Urinary solutes : daily excretion and concentration

For a normal Western type diet, **UREA alone makes up about 40% of all urinary solutes**



Urinary solutes : daily excretion and concentration

For a normal Western type diet, **UREA alone makes up about 40% of all urinary solutes,** and is concentrated in urine 50-100 times above its concentration in the blood



Concentrations in mmol/L		
	UREA	SODIUM
Plasma conc.	5	140
Urine conc.	350	120
Urine/Plasma (range)	70 (30-120)	0.85 (0.30-1.20)

Urinary solutes : daily excretion and concentration

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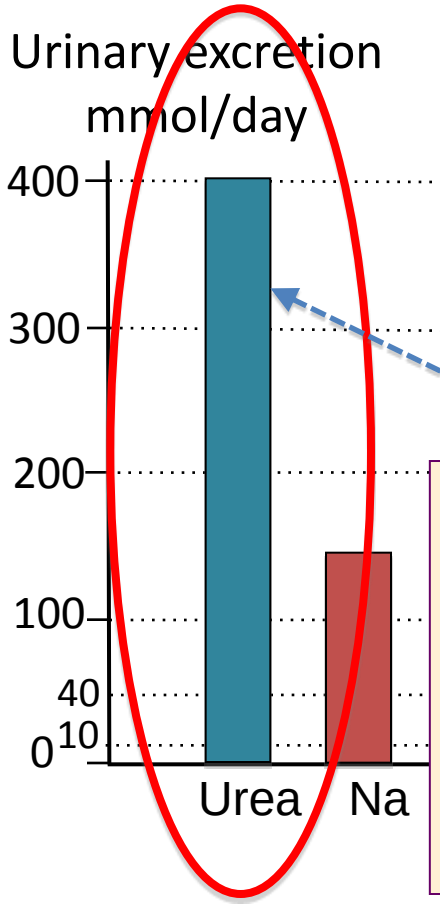


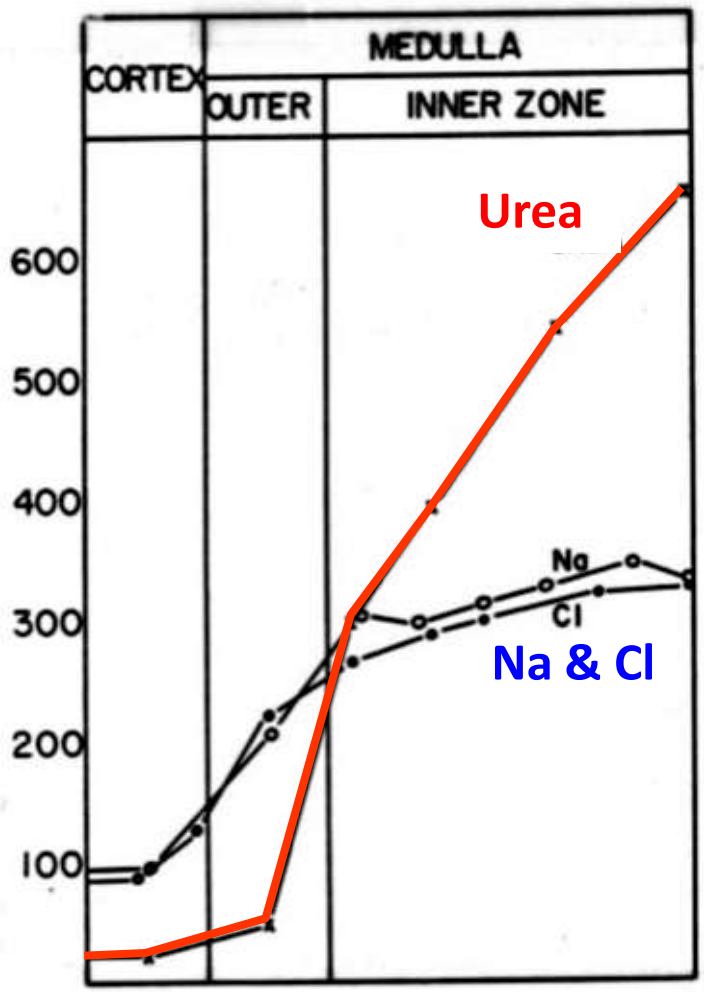
Concentrations in mmol/L

	UREA	SODIUM
Plasma conc.	5	140
Urine conc.	350	120

85 % of the solute-free water reabsorbed by the kidney is devoted to the concentration of urea

Urea gradient in the inner medulla

Solute concentration (mmoles/L)



Outer medulla *Inner medulla*

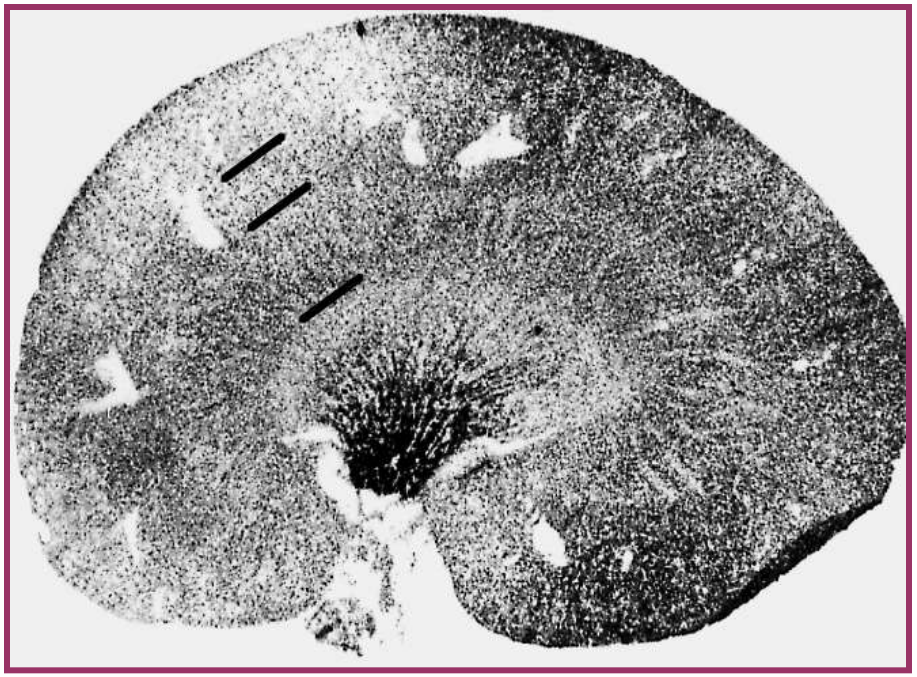
How is **UREA** concentrated in the inner medulla ?

Facilitated urea transporters UT-A1 and UT-A2

In situ hybridization on rat kidney sections

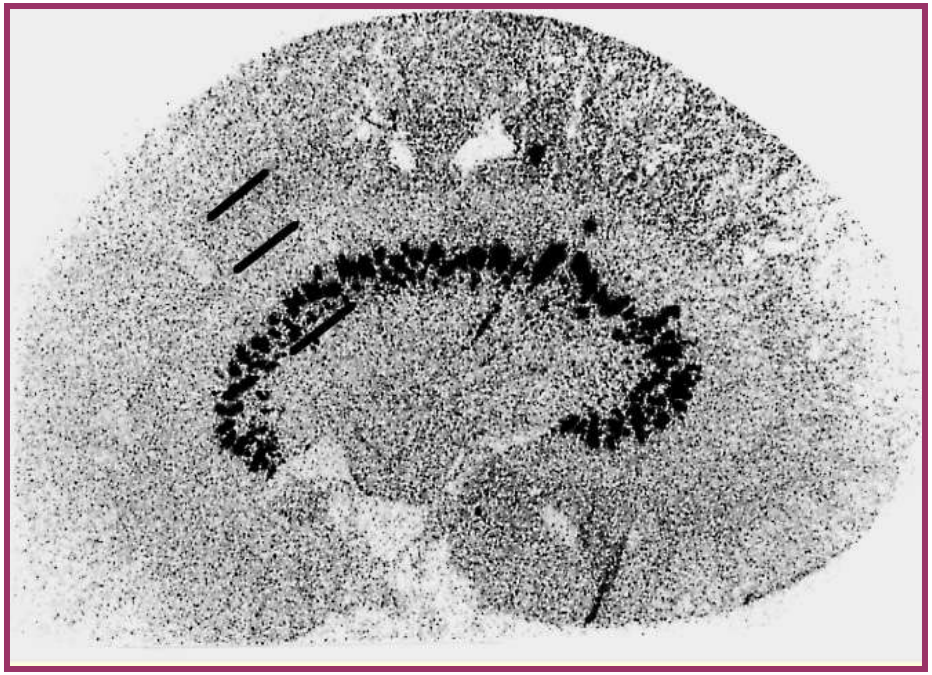
UT-A1

in terminal portion of IMCD
Regulated by vasopressin



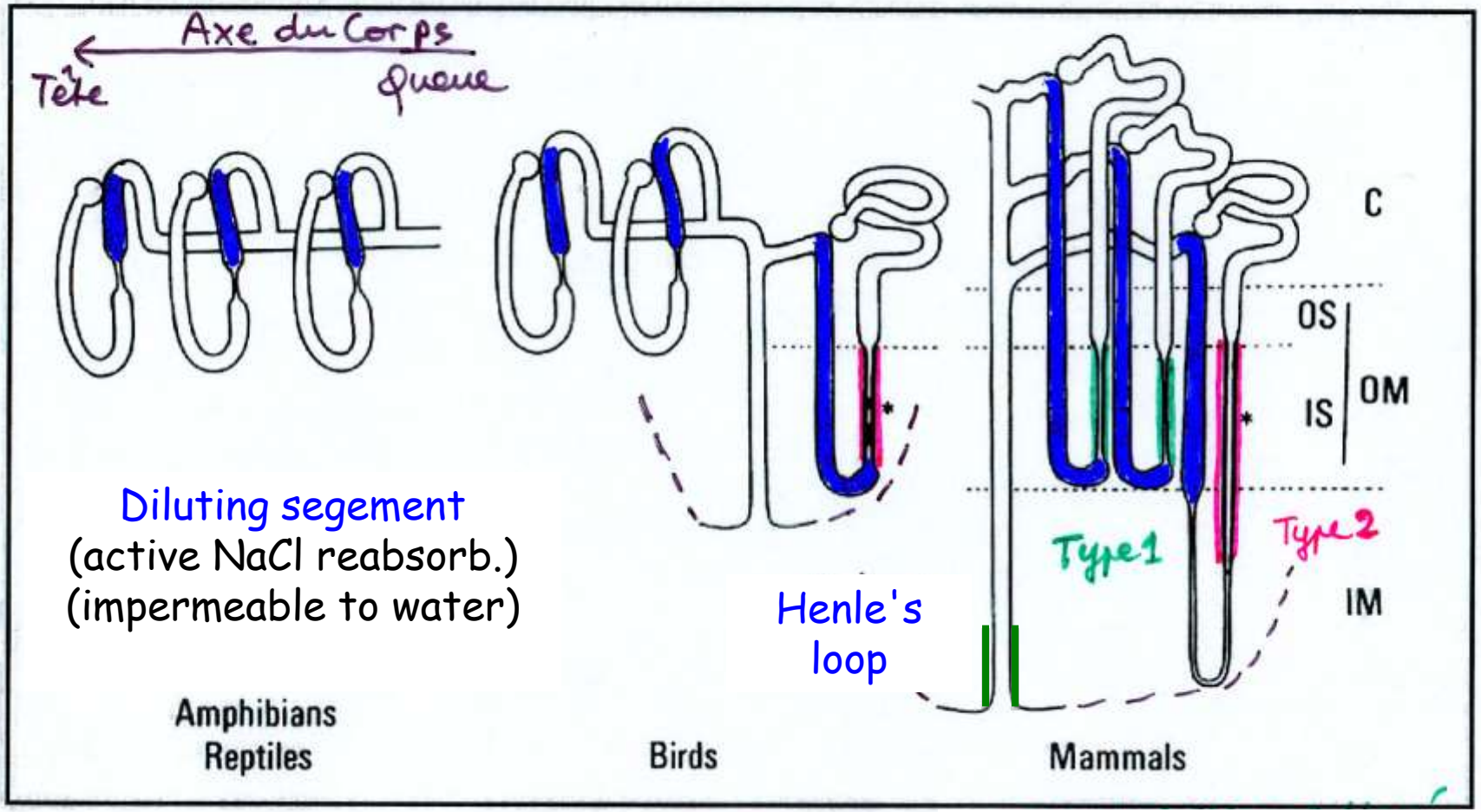
UT-A2

in thin descending limbs
(short looped-nephrons)



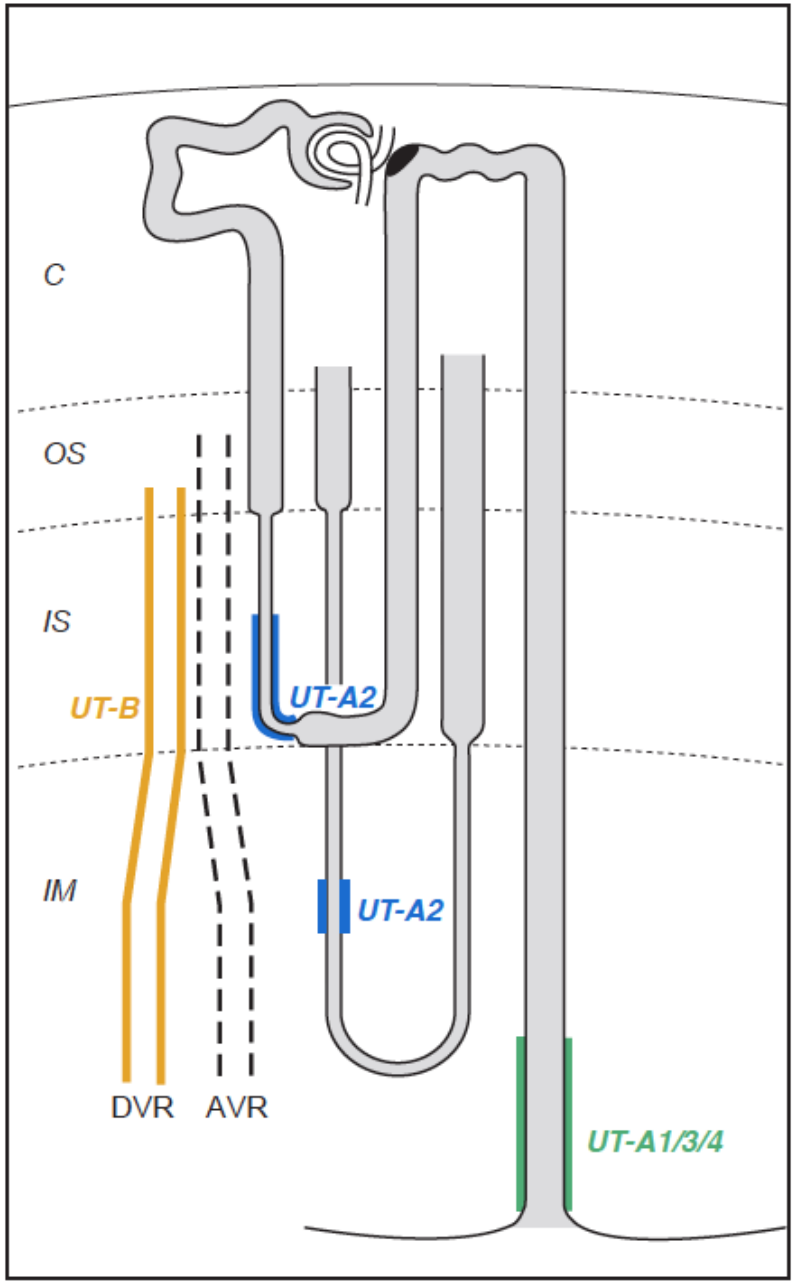
Shayakul et al. J.C.I. 98:2580-2587, 1996

Evolution of the kidney in Vertebrates

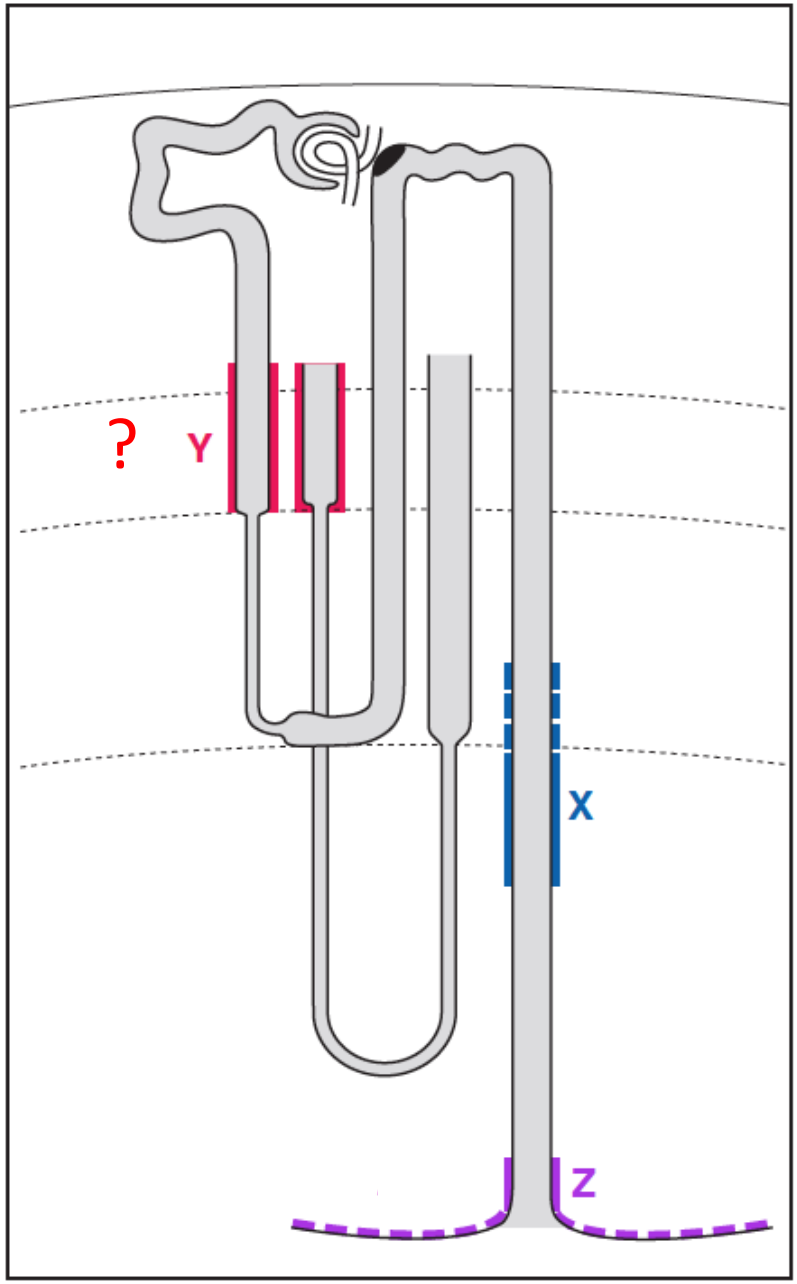


Permeability to urea
Permeability to sodium

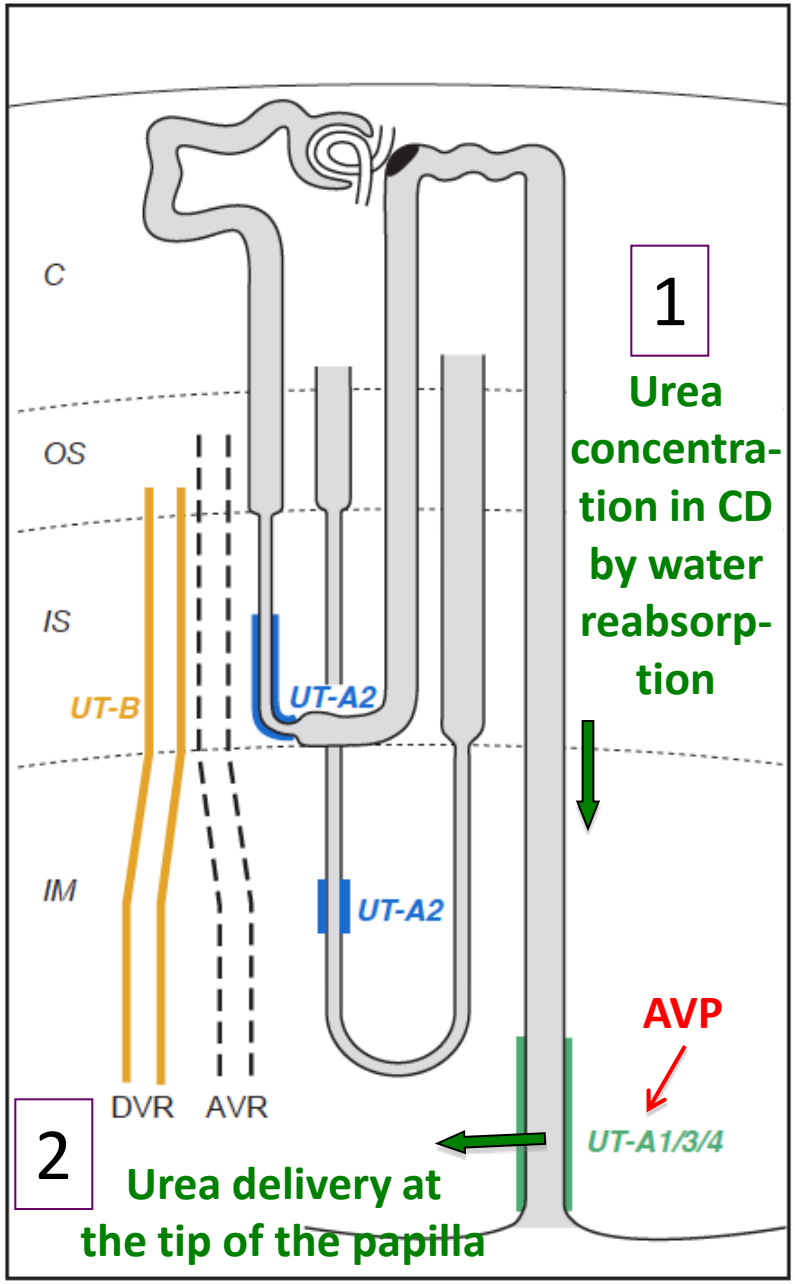
Facilitated urea transporters



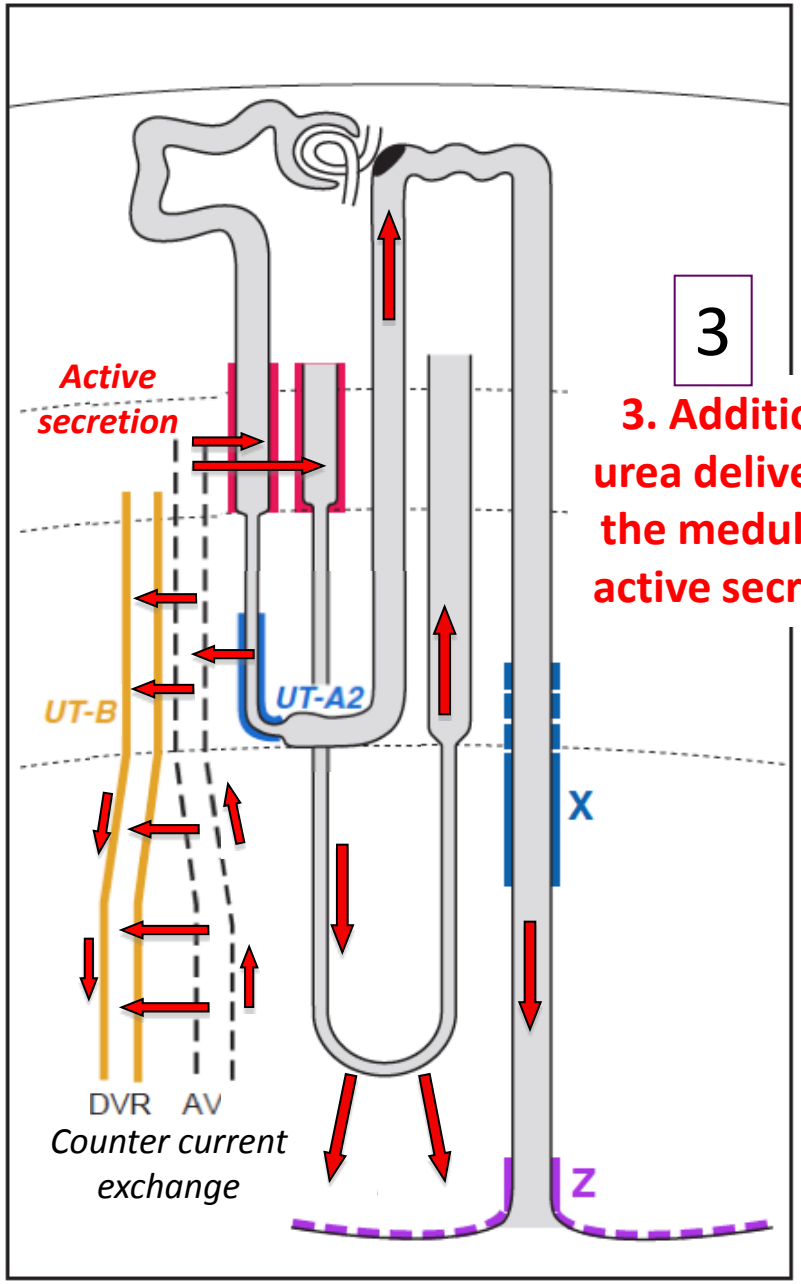
Active urea transporters



Facilitated urea transporters

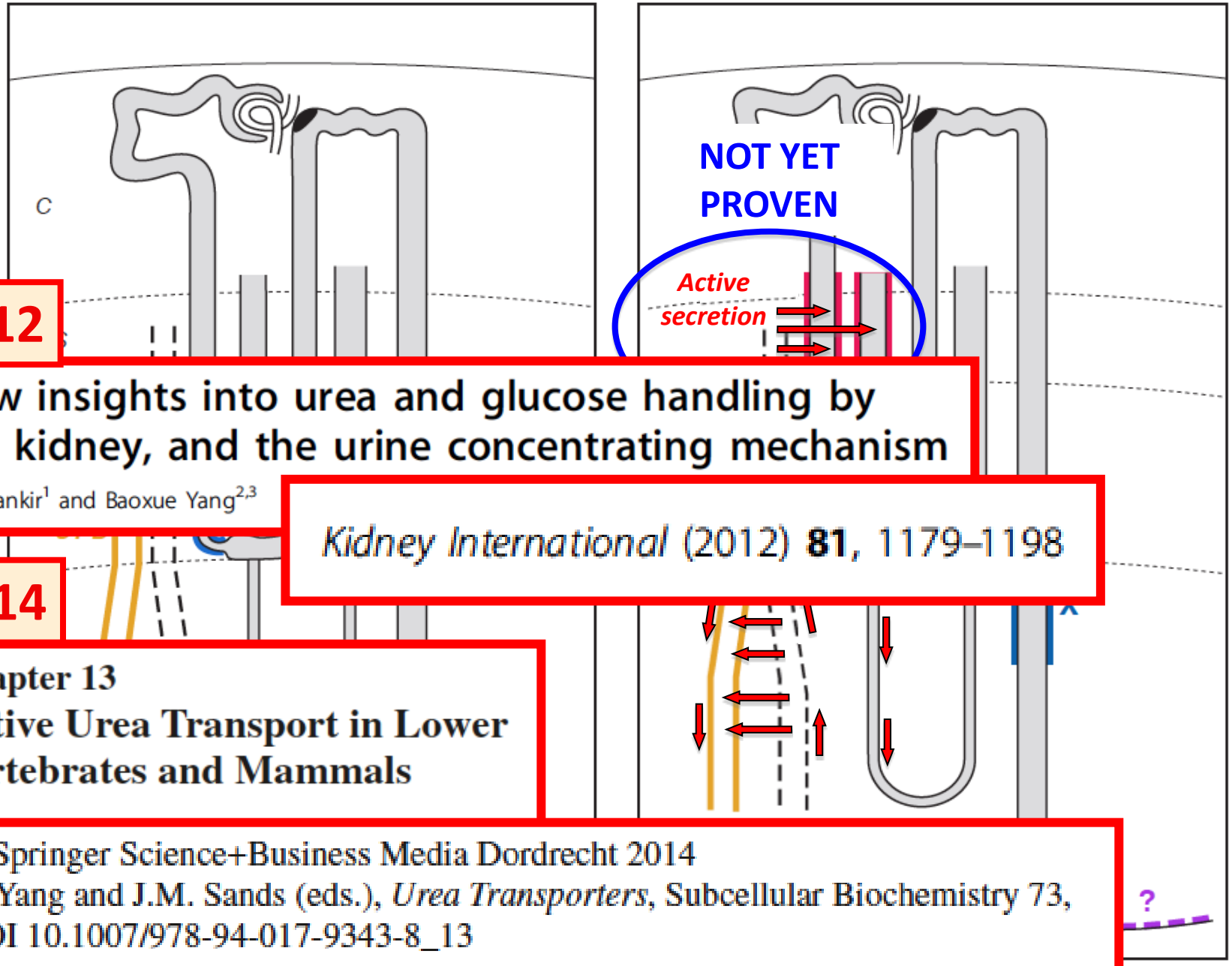


Active urea transporters



Facilitated urea transporters

Active urea transporters



2012

New insights into urea and glucose handling by the kidney, and the urine concentrating mechanism

Lise Bankir[1] and Baoxue Yang[2,3]

Kidney International (2012) **81**, 1179–1198

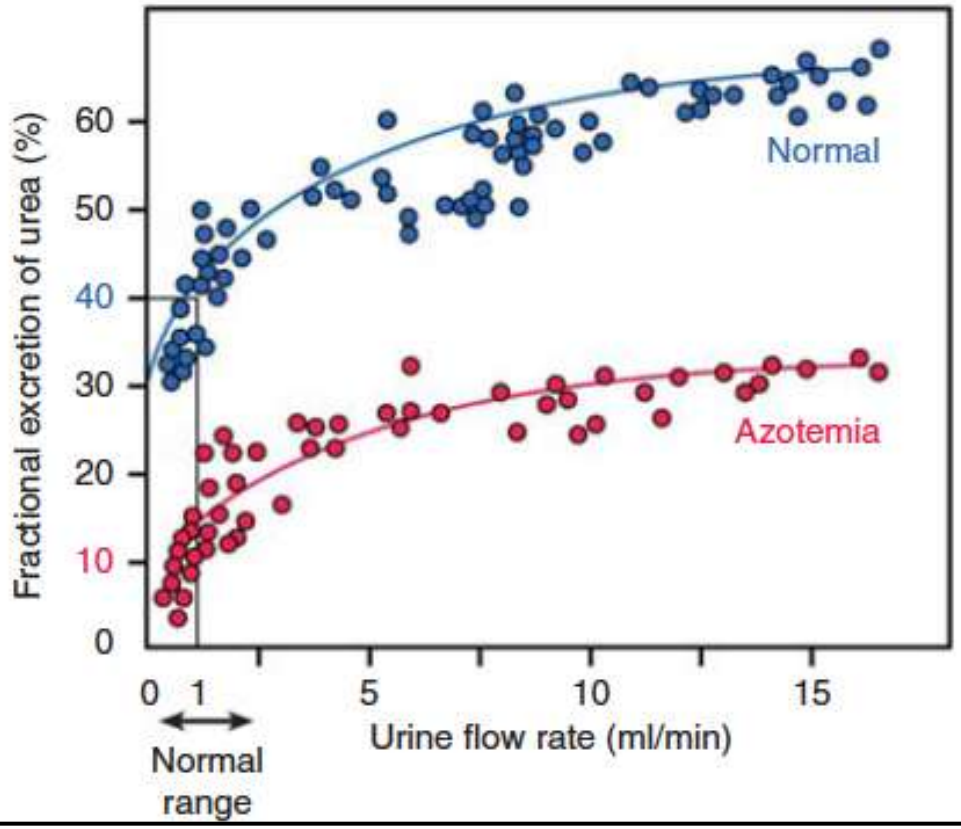
2014

Chapter 13
Active Urea Transport in Lower Vertebrates and Mammals

© Springer Science+Business Media Dordrecht 2014
B. Yang and J.M. Sands (eds.), *Urea Transporters*, Subcellular Biochemistry 73,
DOI 10.1007/978-94-017-9343-8_13

Familial azotemia without renal failure

- Plasma urea concentration 3 to 5-fold above normal
- Markedly reduced fractional excretion of urea
- No sign of renal dysfunction



If you know such cases, please let me know !

The Renal Medulla : Outline

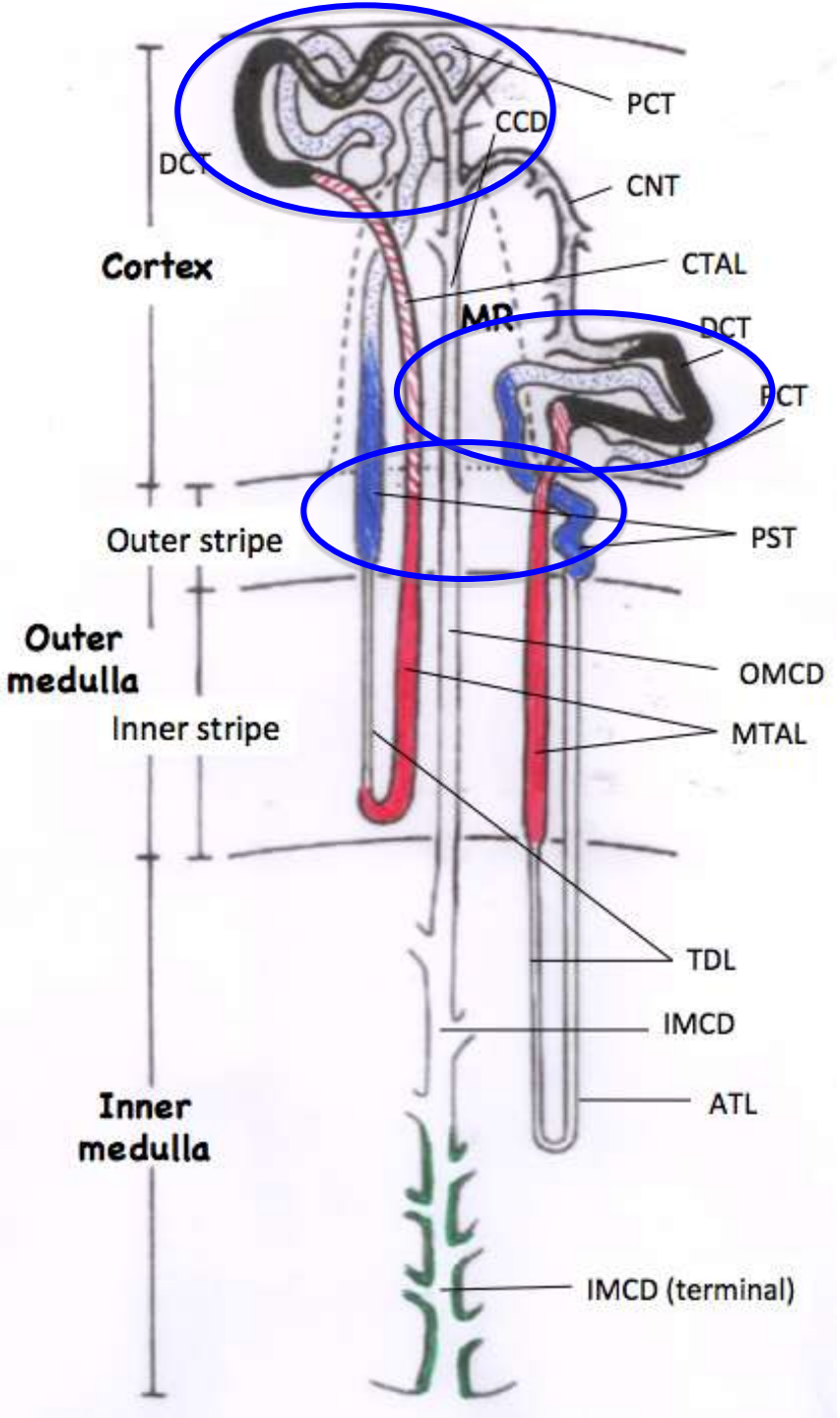
1. Anatomy / Vascularisation

2. Urine concentration

3. **Axial heterogeneity of some tubule segments**

Proximal tubule

Special situation of the
medullary pars recta in the
outer medulla



Proximal tubule

LONGITUDINAL heterogenity

- **Convoluted part (S1, S2)**
- **Straight part (S2, S3)**

Different vascular environments
Differences in epithelium

INTERNEPHRON heterogenity

- **Superficial nephrons**
- **Deep nephrons**

Deep nephrons have bigger glomerulus, longer convoluted tubule, tortuous pars recta, higher GFR.
Their efferent arteriole provides blood flow to the medulla

Vascular environment of Pars Recta in the Outer Stripe

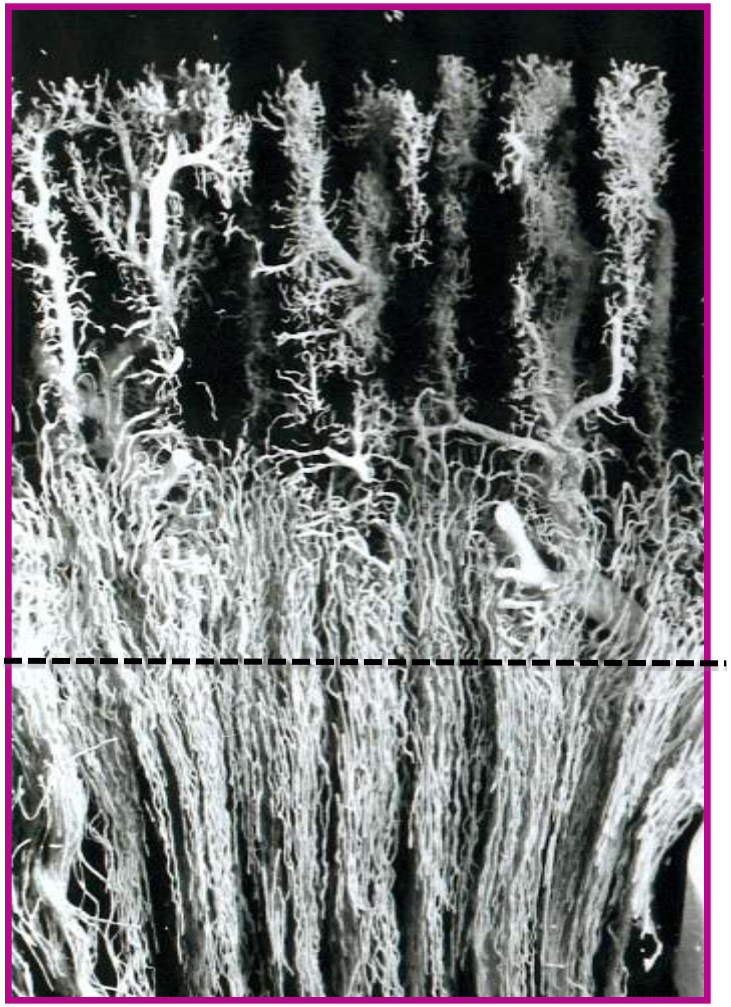
Filling of the venous vasculature

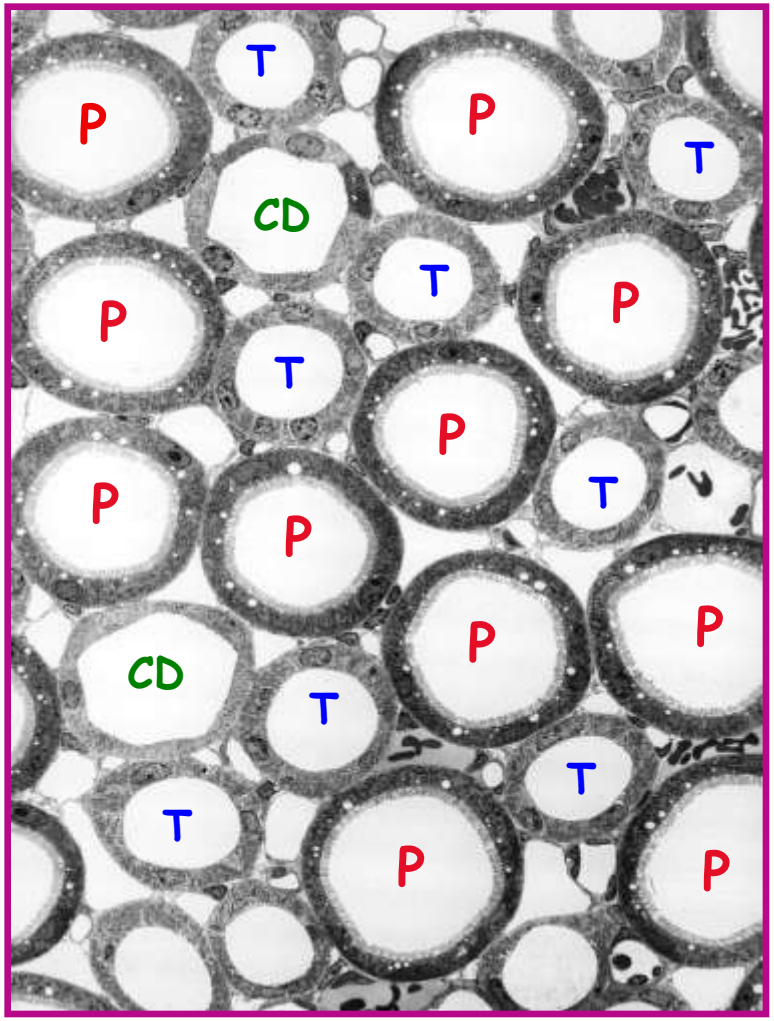
Cross section through OS (histology)

Cortex

OS

IS





P = Pars Recta T = TAL CD = Collecting duct

Vascular environment of Pars Recta in the Outer Stripe

Filling of the venous vasculature

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OS

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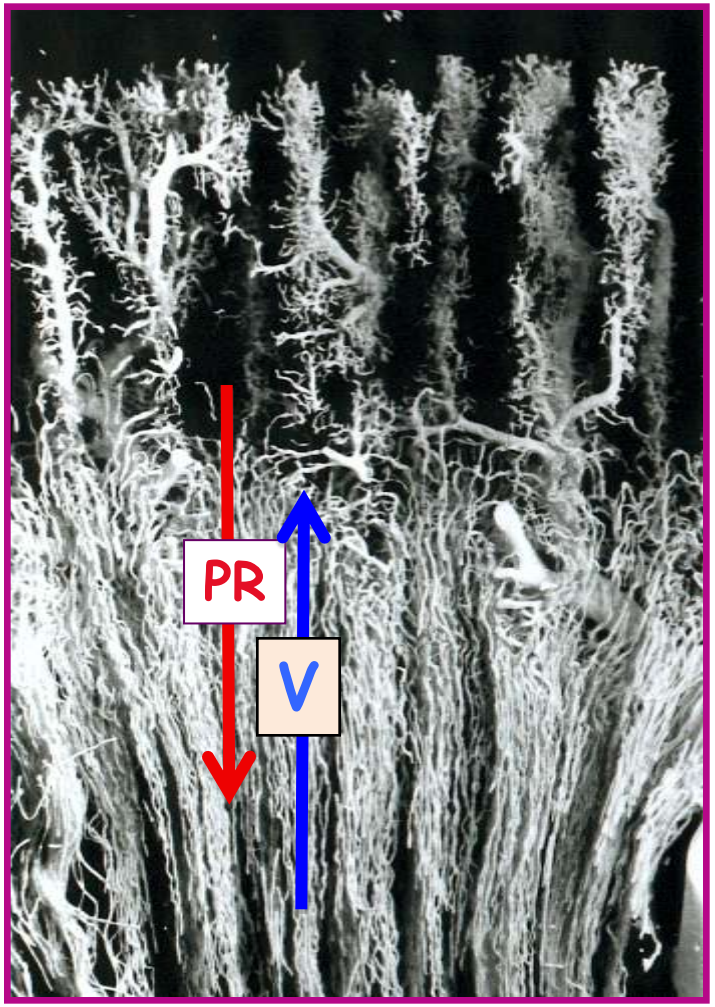
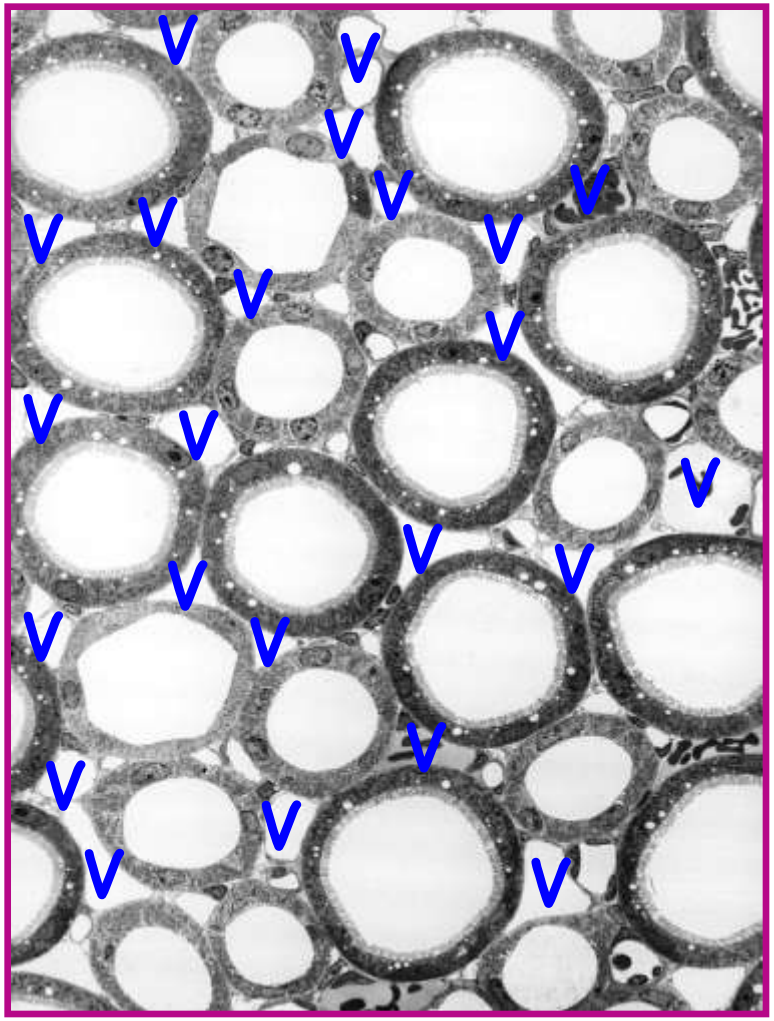
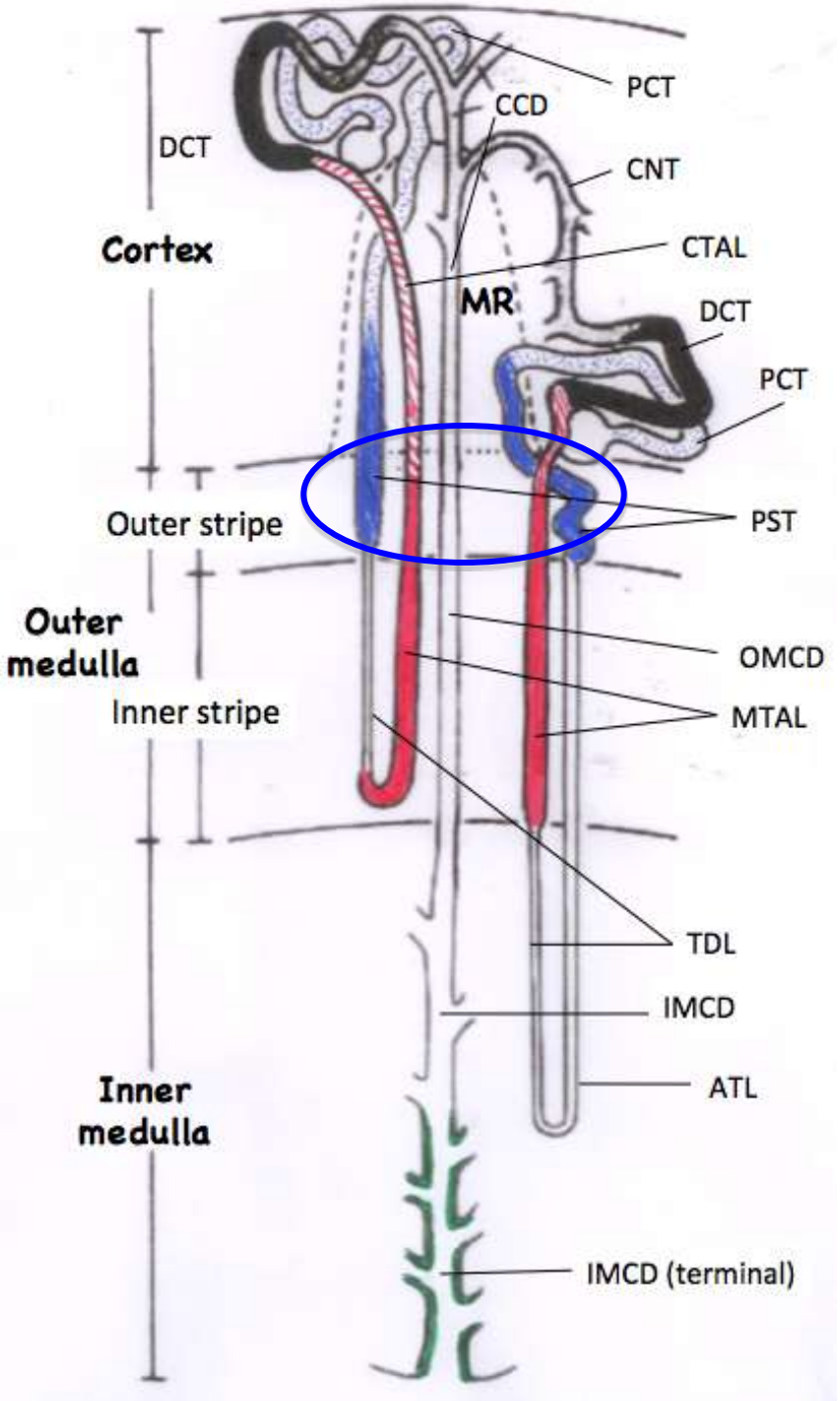




PR = Pars Recta V = Venous, Ascending Vasa Recta



Proximal tubule

The **pars recta** is mostly a **SECRETORY** segment

- Hippurate (PAH)
- Organic acids, uric acid
- Nucleotides
- Xenobiotics – Drugs
- Urea ???

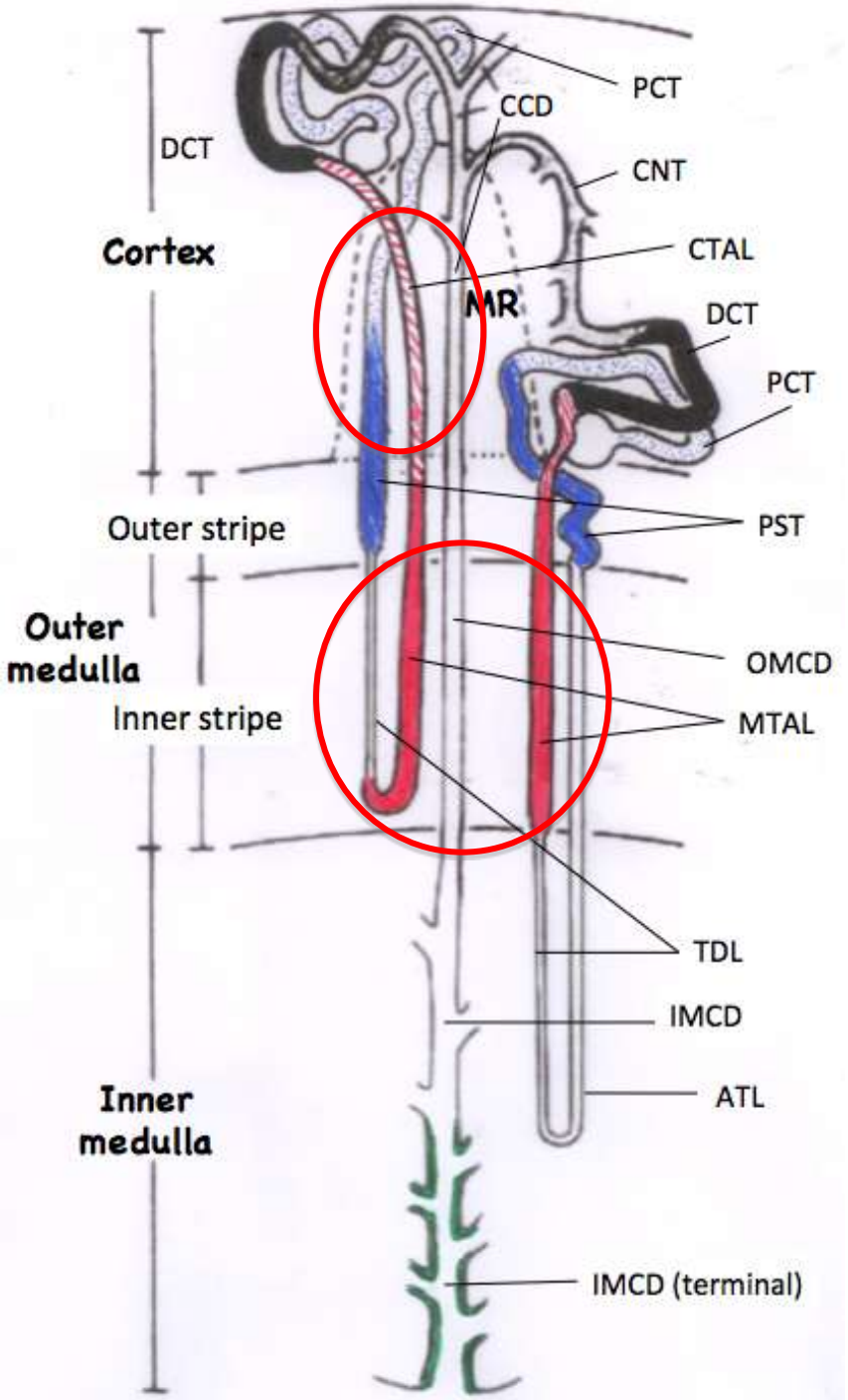
Water follows the solutes (increases the flow in the loop)

Improved excretion (on top of filtration)

But also **accumulation of toxic products** when no transporter on luminal side (ex. **Cisplatin**)

Thick ascending limb

Both, major **axial heterogeneity** and **inter-nephron heterogeneity**



Thick ascending limb
= Straight distal tubule

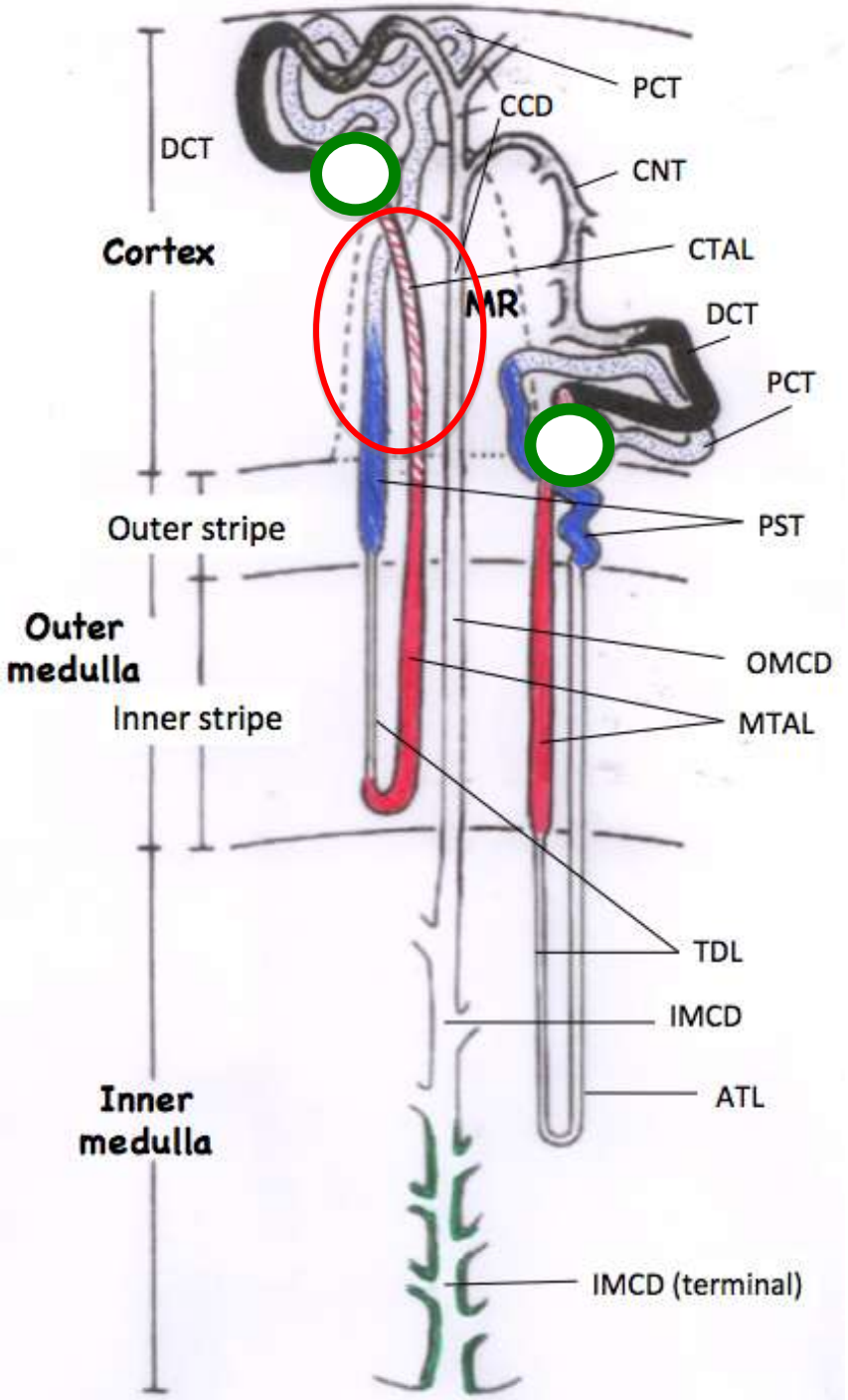
Strong
AXIAL HETEROGENITY
with respect to anatomy, environment, and function

Medullary TAL

- Runs in **hyper-osmotic** medulla
- Faces thin descending segments
- Relatively low med. blood flow
- **Contributes to building of the medullary solute gradient**

Cortical TAL

- Runs in **iso-osmotic** cortex
- No thin segment in parallel
- High cortical blood flow
- **Contributes to urine dilution**



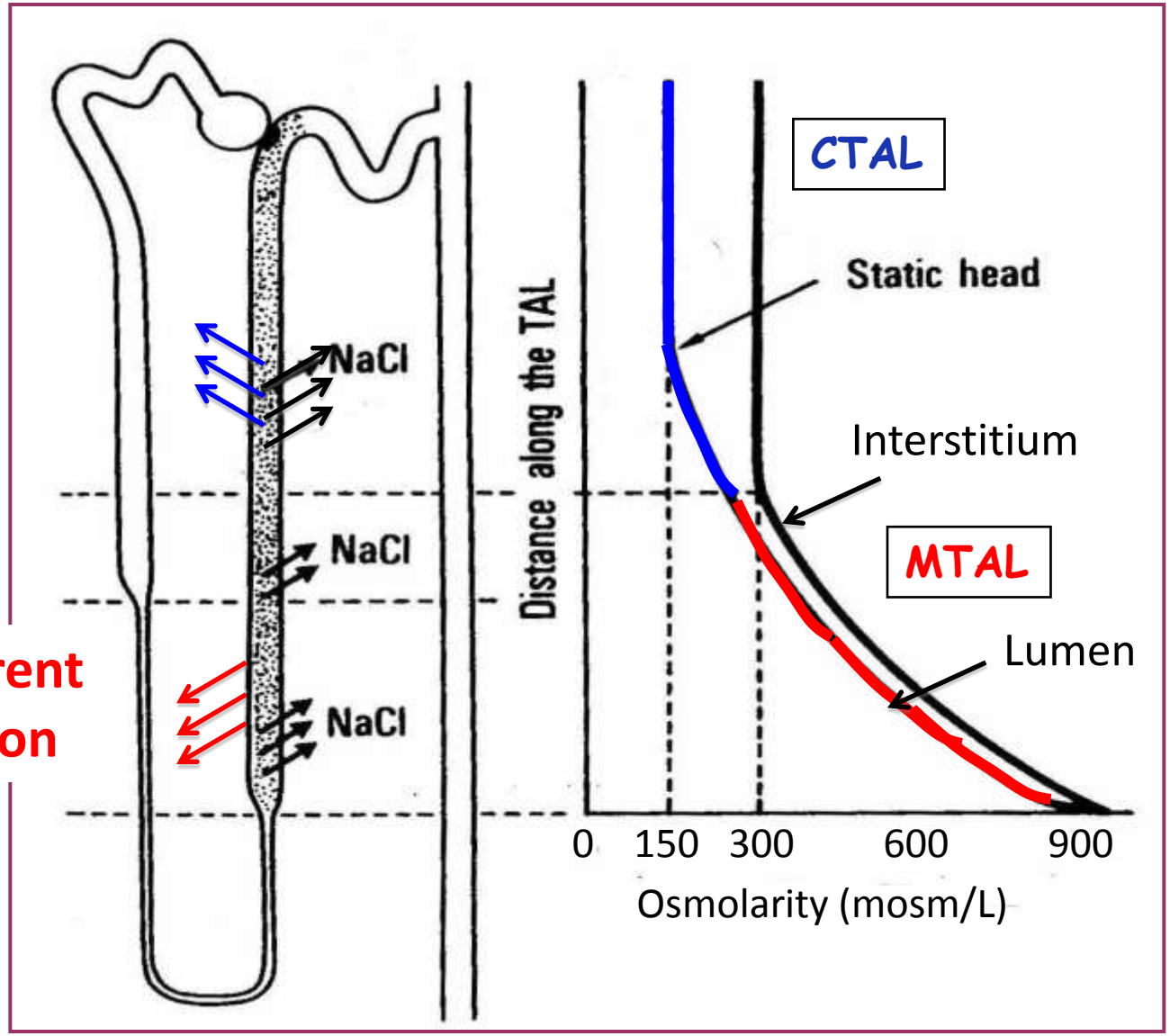
Thick ascending limb
= Straight distal tubule

Strong **INTERNEPHRON HETEROGENITY**

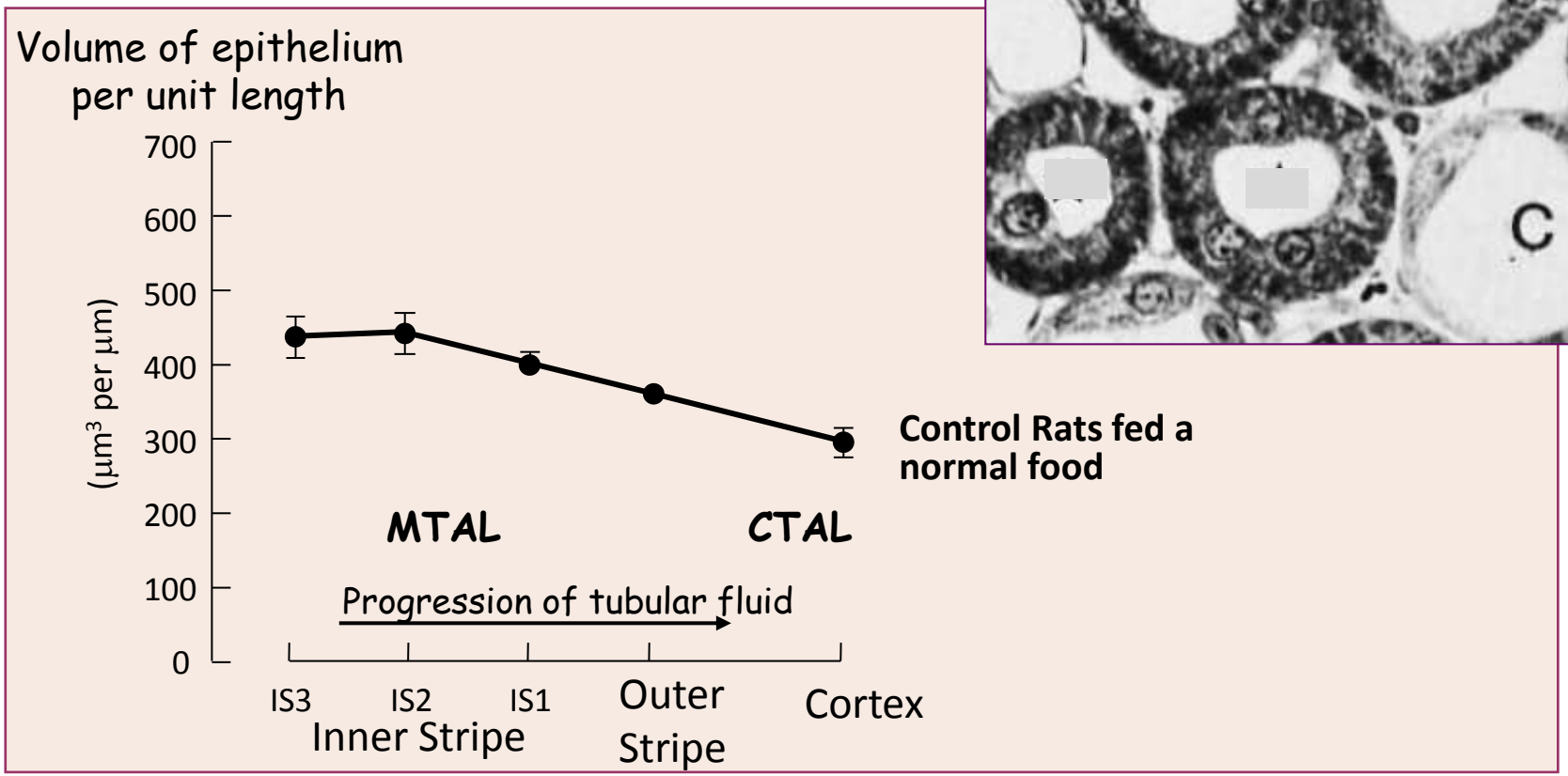
- **LONG cortical TAL**
  in superficial nephrons
- **NO cortical TAL**
  in deep nephrons

Consequences on the composition of tubular fluid at the macula densa, and thus on **tubulo-glomerular feedback control of GFR**

Axial heterogeneity of the Thick Ascending Limb

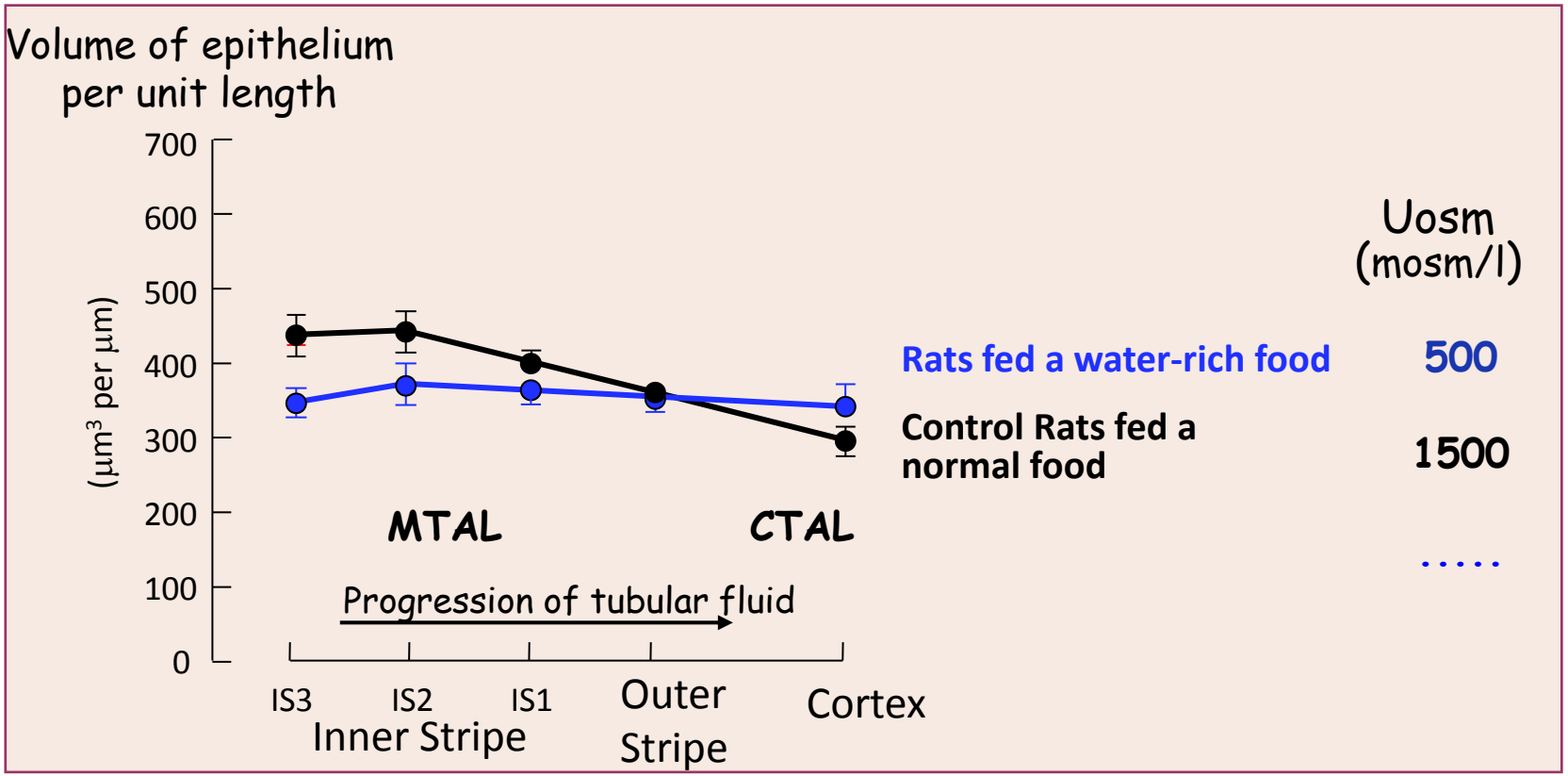


MTAL and CTAL adaptation to different levels of urine concentration in rats



Bankir, Pflugers Arch. 412:42-53, 1988

MTAL and CTAL adaptation to different levels of urine concentration in rats



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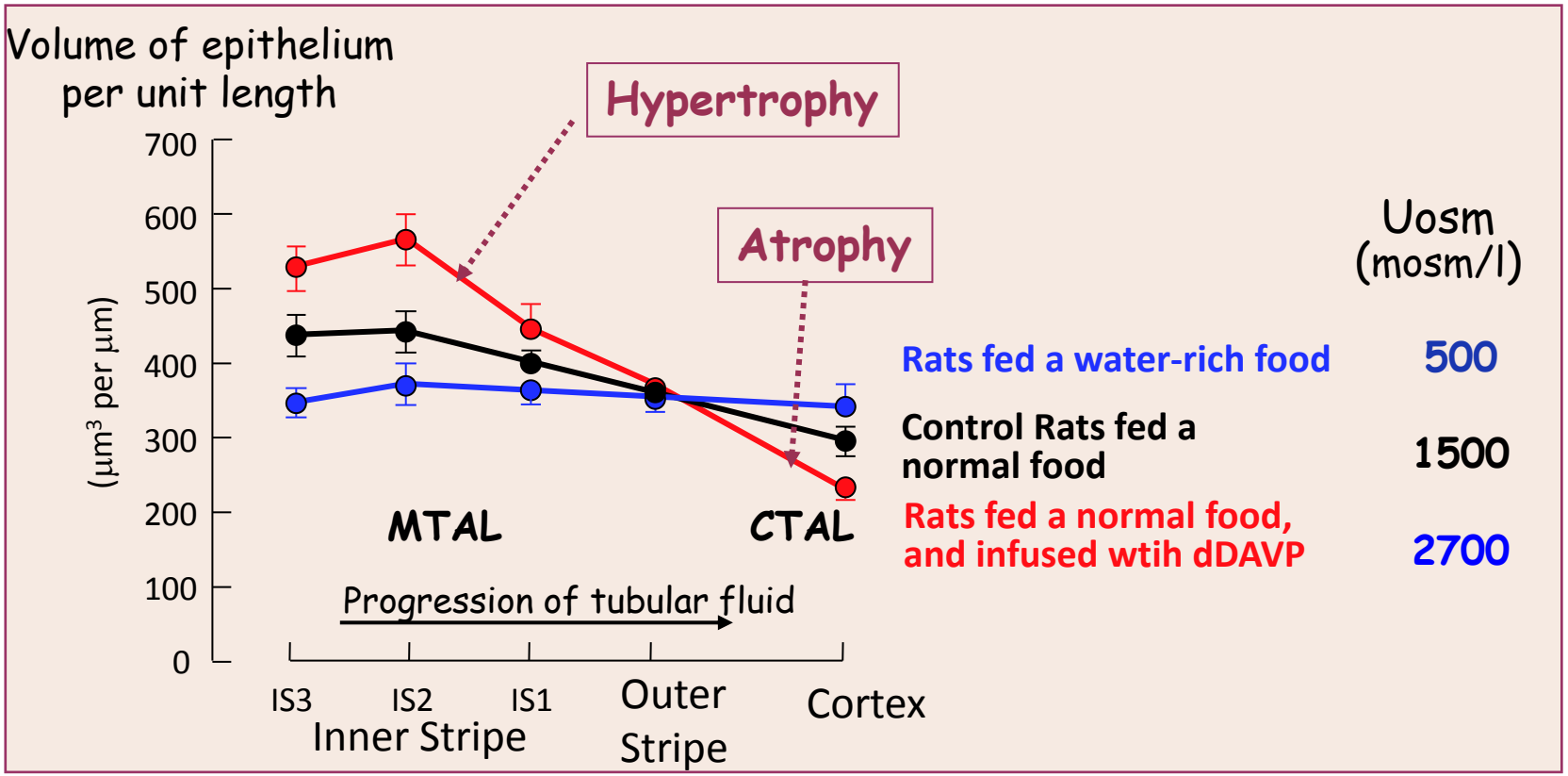
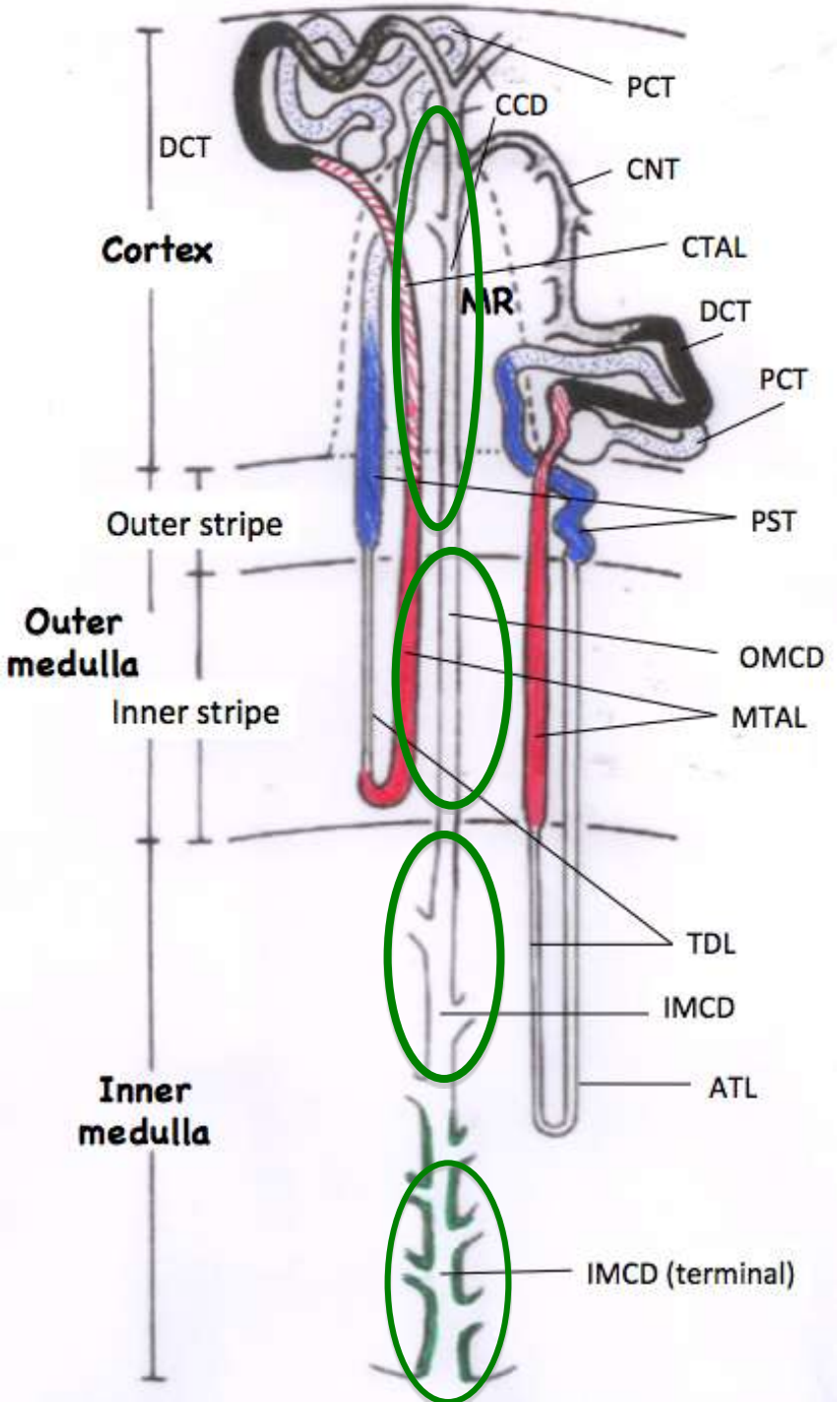


Bankir, Pflugers Arch. 412:42-53, 1988

Collecting duct

Marked **heterogeneity** along the whole cortico-papillary axis

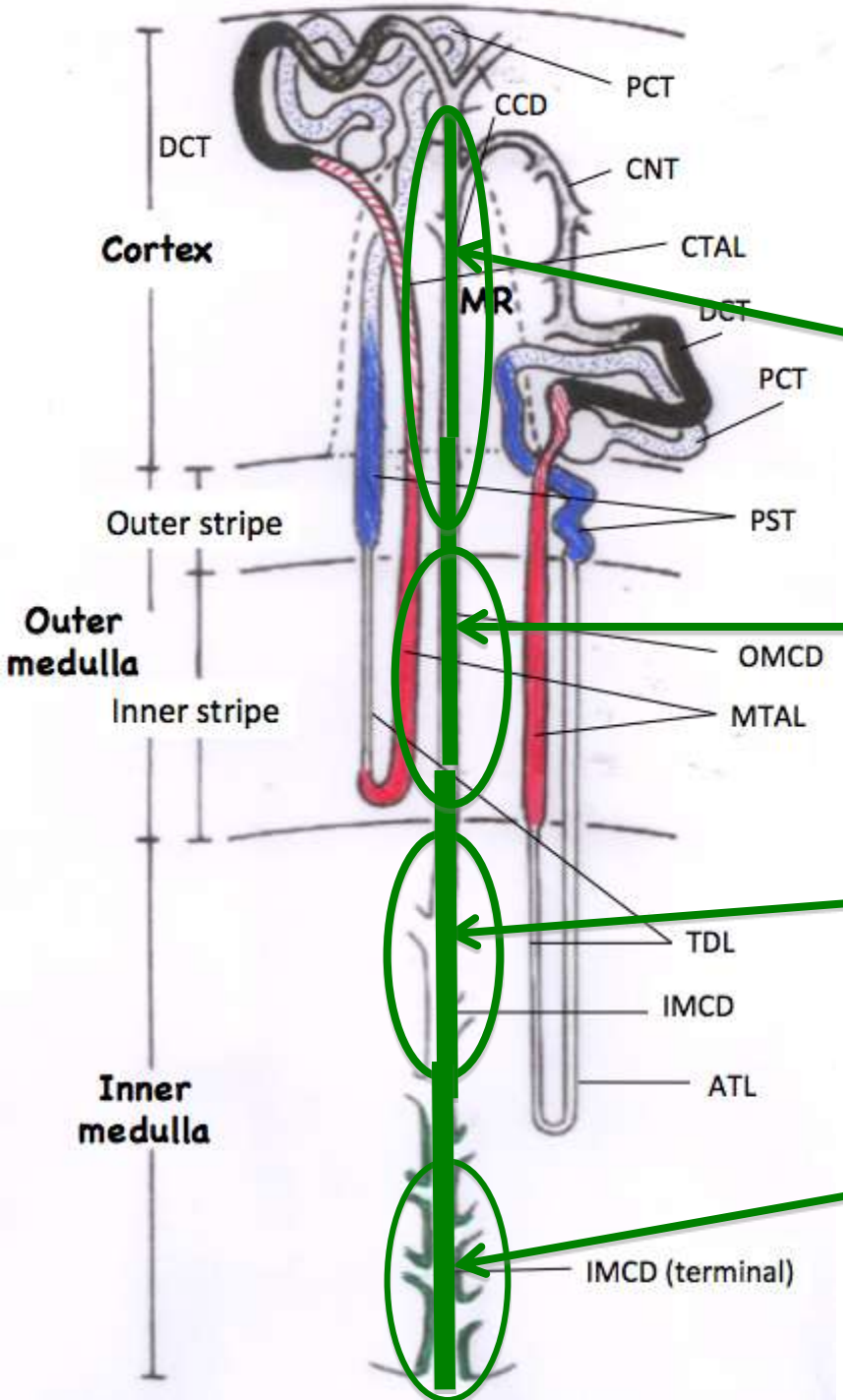


Collecting duct

AXIAL HETEROGENEITY

- Cortical CD + OS CD
- Outer medullary CD in IS
- Early inner medullary CD
- Terminal inner medullary CD

Collecting duct



AQP2 luminal along the whole CD
AQP4 basolateral along the whole CD

Importance of **ENaC** (and possibly **AQP3**) in the ratio between sodium and urea in the urine

Major role in acid-base balance
Major hypertrophy on a low K diet

Active urea reabsption (only in herbivores and in rats fed a low protein diet. Neglibeable in humans)

UT-A1 / UT-A3
Important contribution to the urine concentrating mechanism

ANP receptors
Possible role in the ratio between sodium and urea in the urine

Adverse consequences of urine concentration

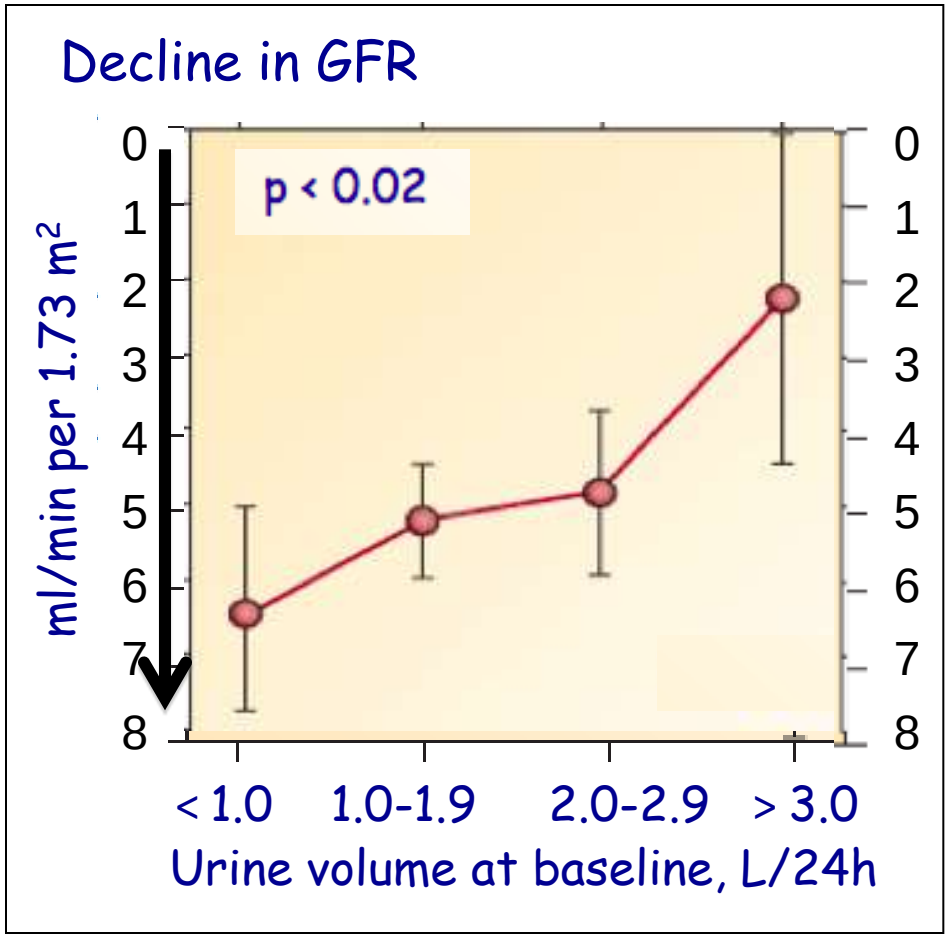
- It reduces the fractional excretion of some solutes (sodium, urea, creatinine, etc.....) and increases the plasma concentration of several waste products

- It induces glomerular hyperfiltration (and the associated vicious circle) and increases urinary albumin excretion

It contributes to salt-sensitive hypertension (due to its effect on ENaC)

- It contributes to progression of CKD and diabetic nephropathy (and to ADPKD but by a different mechanism)

GFR decline in a **general population** according to 24 h urine volume



Adapted after Clark et al, CJASN, 2011

Follow-up = 5.7 years in 2,148 participants

GFR decline was far more rapid in those with a low urine volume.

Adjusted for :

- age, gender,
- baseline estimated GFR,
- dipstick protein,
- medication for hypertension,
- diabetes
- cardiovascular disease

Adverse consequences of urine concentration

Bankir, Bouby and Ritz
Vasopressin: a novel target for the prevention and retardation of kidney disease?
Nature Reviews Nephrology, 9, 223–239, 2013

Bankir, Roussel and Bouby
Protein- and diabetes-induced glomerular hyperfiltration: role of glucagon, vasopressin, and urea.
Am J Physiol Renal Physiol 309: F2–F23, 2015

Importance of renal medulla and water conservation in EVOLUTION

Lack of WATER

↓

Dehydration

↓

Life-threatening in the short-term (over days)

Good adaptation to WATER CONSERVATION

↓

Decline in kidney function and Hypertension
Long-term consequences (decades)
= after the period of reproduction

EVOLUTION has favored water conservation .....

because the long-term consequences ....

do not exert any pressure on natural selection

The Renal Medulla and urine concentration

Take home messages

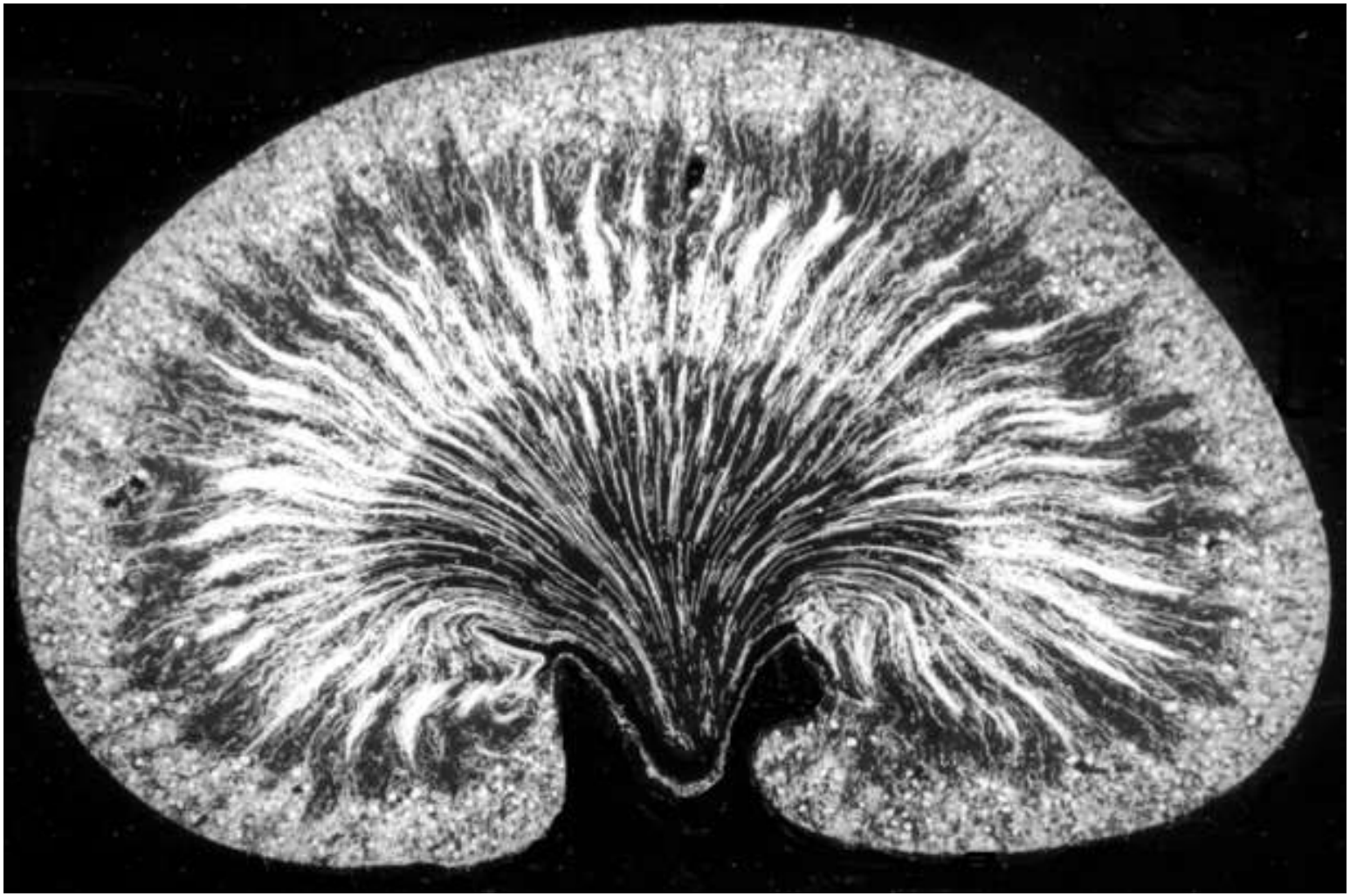
1. Three different zones with strong spatial and vascular compartmentation

2. Axial and inter-nephron heterogeneity of nephron and collecting duct subsegments

3. Possible consequences on tubulo-glomerular feedback control of glomerular filtration rate

4. Possible consequences on blood pressure, progression of CKD, diabetic nephropathy, etc....

Questions welcome, if any



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