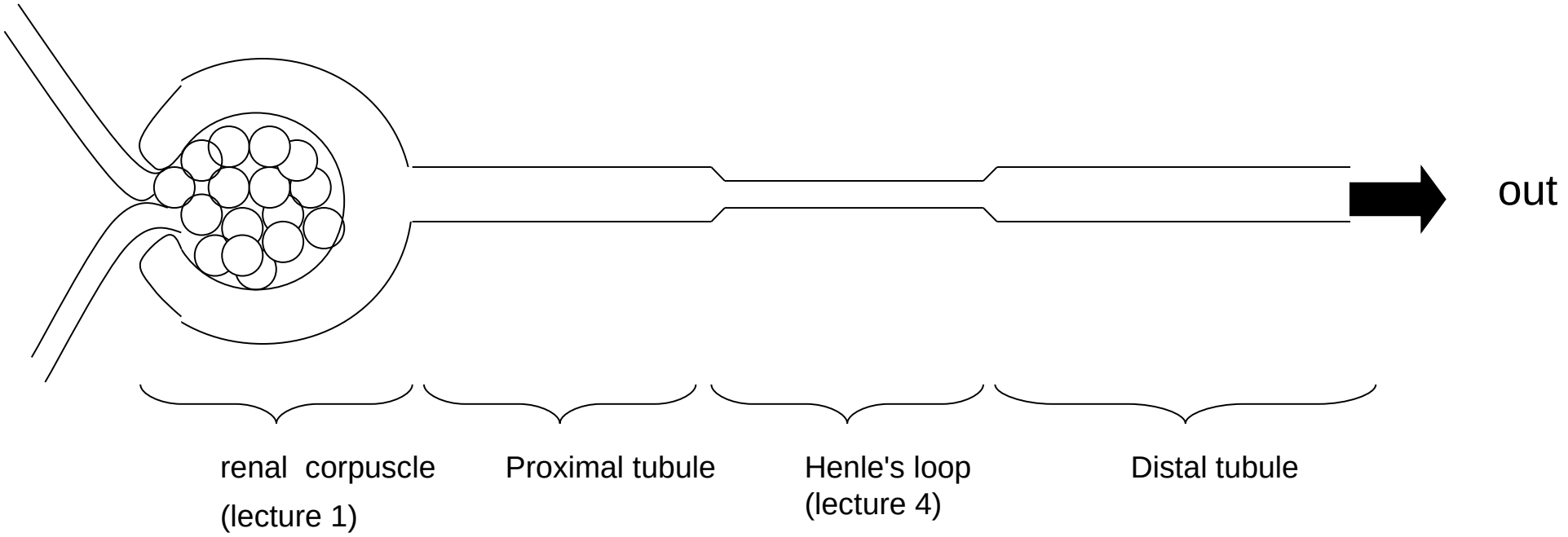
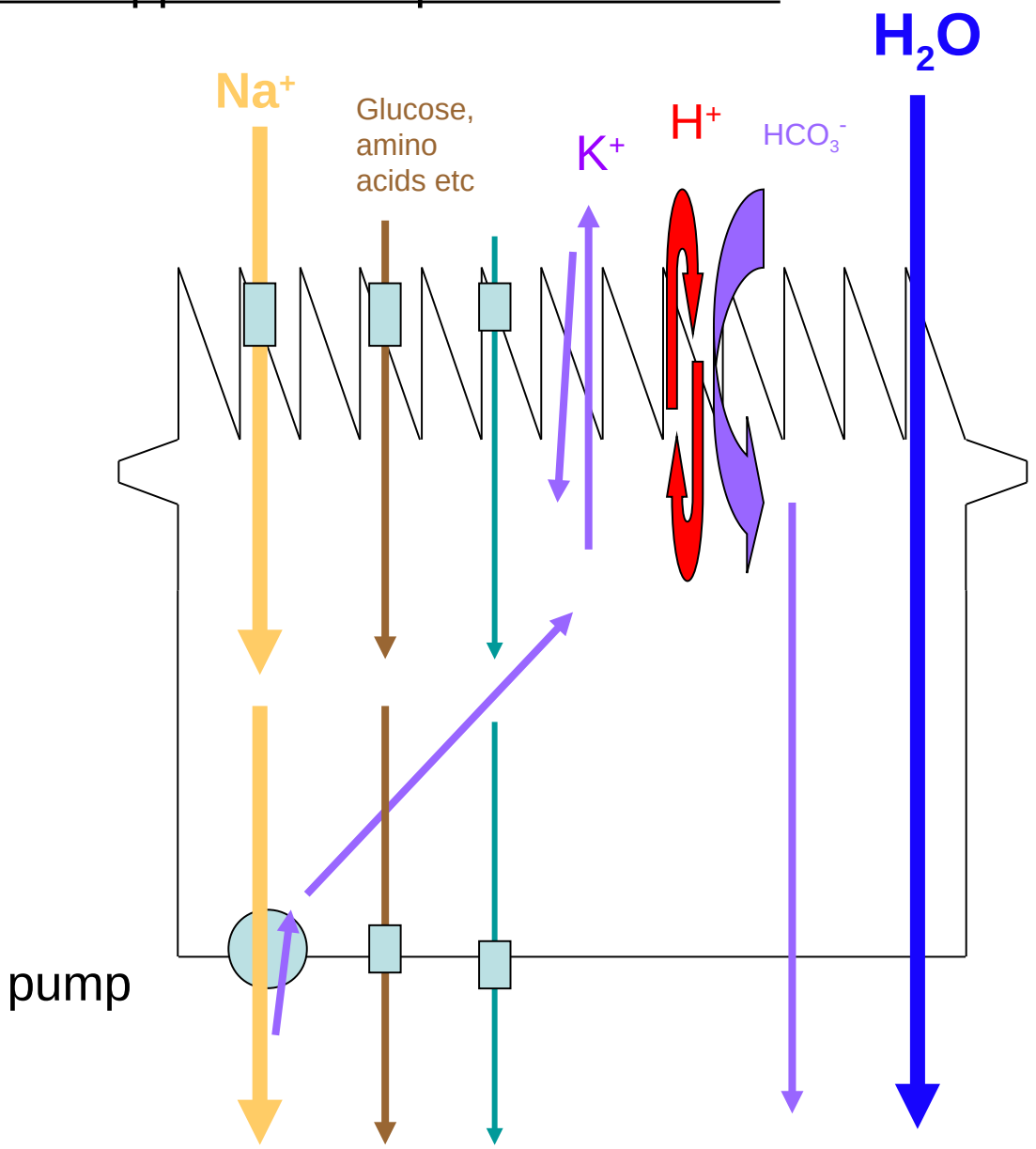
The rest of the nephron is divided into 3 main zones:

(each is subdivided into segments, but we don't need to worry about that yet)



What happens in the proximal tubule?



Sodium is pulled through by the basal pump

Glucose, amino acids etc are pulled through by the sodium gradient.

Phosphate etc are pulled through by the sodium gradient.

Potassium is dumped into tubule lumen, again due to the basal pump

HCO_3^- is recovered, with a bit of H^+ cycling, again powered by the sodium gradient.

All of this solute movement tries to lower the osmolarity of the tubule, so water flows passively from the tubule to counteract this.

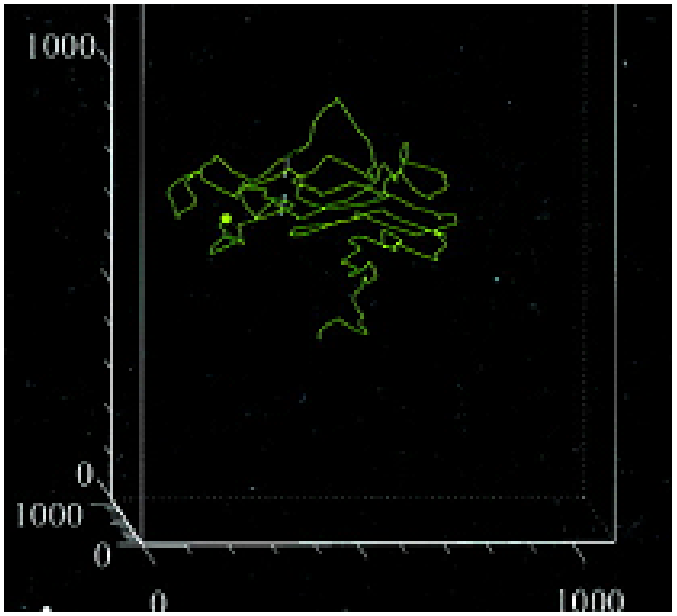
Chloride also leaves passively to stop its concentration rising in the tubule.

(through aquaporins)

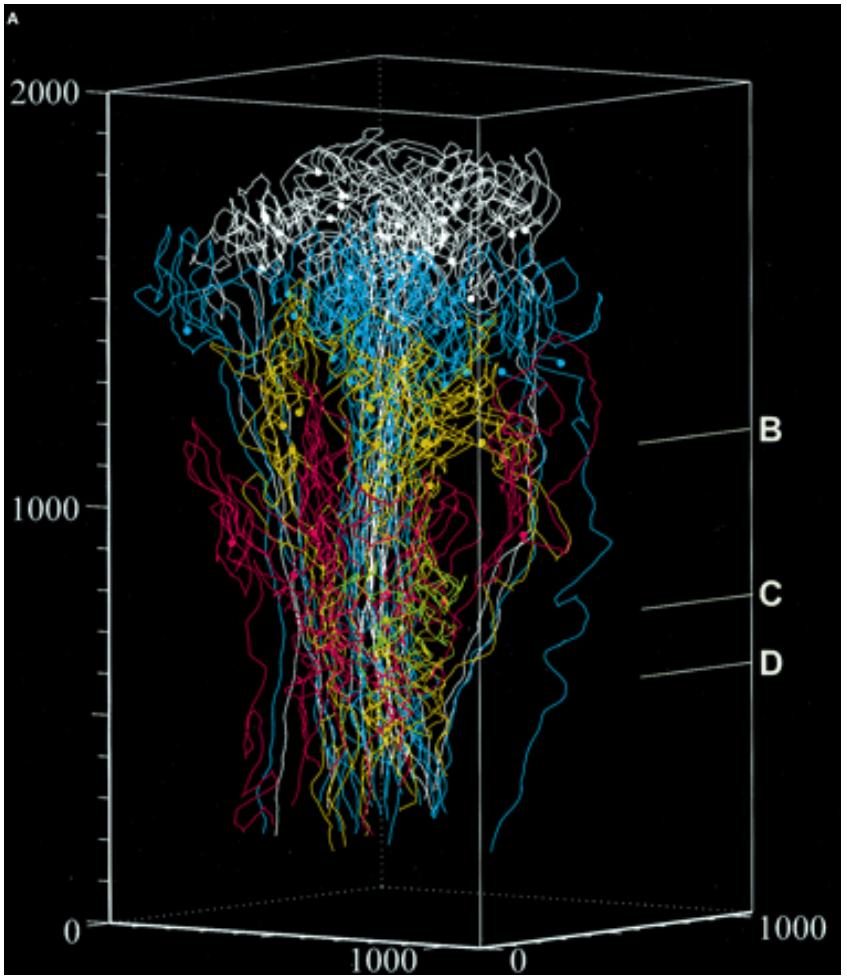
We need quite a lot of surface area to do this well:

1) Microvilli

2) Pack a lot of length into a small space



One tubule (mouse)



53 tubules (mouse)

From : Zhai XY, Birn H, Jensen KB, Thomsen JS, Andreasen A, Christensen EI. (2003) Digital three-dimensional reconstruction and ultrastructure of the mouse proximal tubule. J Am Soc Nephrol. 14(3):611-9

→ Proximal convoluted tubule (PCT)

So what has the proximal tubule achieved?

Recovery of sodium, chloride, phosphate, calcium etc	**YES** (65%)
Recovery of water	**YES** (some)
Concentration of urine	**NO** (still roughly iso-osmotic)
Control of acid/base	**NO** (or only slightly)

But this is not enough - we need to concentrate the urine and recover more ions

Renal blood flow 1.2L/min = 1700L/day

Prox tubule recovery 65% so loss would be 35% of 1700L = 595L

A human actually drinks around 2L/day, and eats 3g salt

(This teaspoon of salt would normally be in other foods; no need to add)

But this is not enough - we need to concentrate the urine and recover more ions

Prox tubule recovery 65% so loss would be 35% of 1700L = 595L

A human actually drinks around 2L/day

If we could not concentrate urine, we would need to drink 595L/day and eat 2kg salt →

But this is not enough - we need to concentrate the urine and recover more ions

Prox tubule recovery 65% so loss would be 35% of 1700L = 595L

A human actually drinks around 2L/day

If we could not concentrate urine, we would need to drink 595L/day

And there's not much water or salt around in humans' ancestral habitat

(Museum display representation of early H sapiens.)

So - what tools have we got to concentrate urine?

1) We do NOT have a water pump !

2) We do have the Na^{+}/K^{+} ATPase

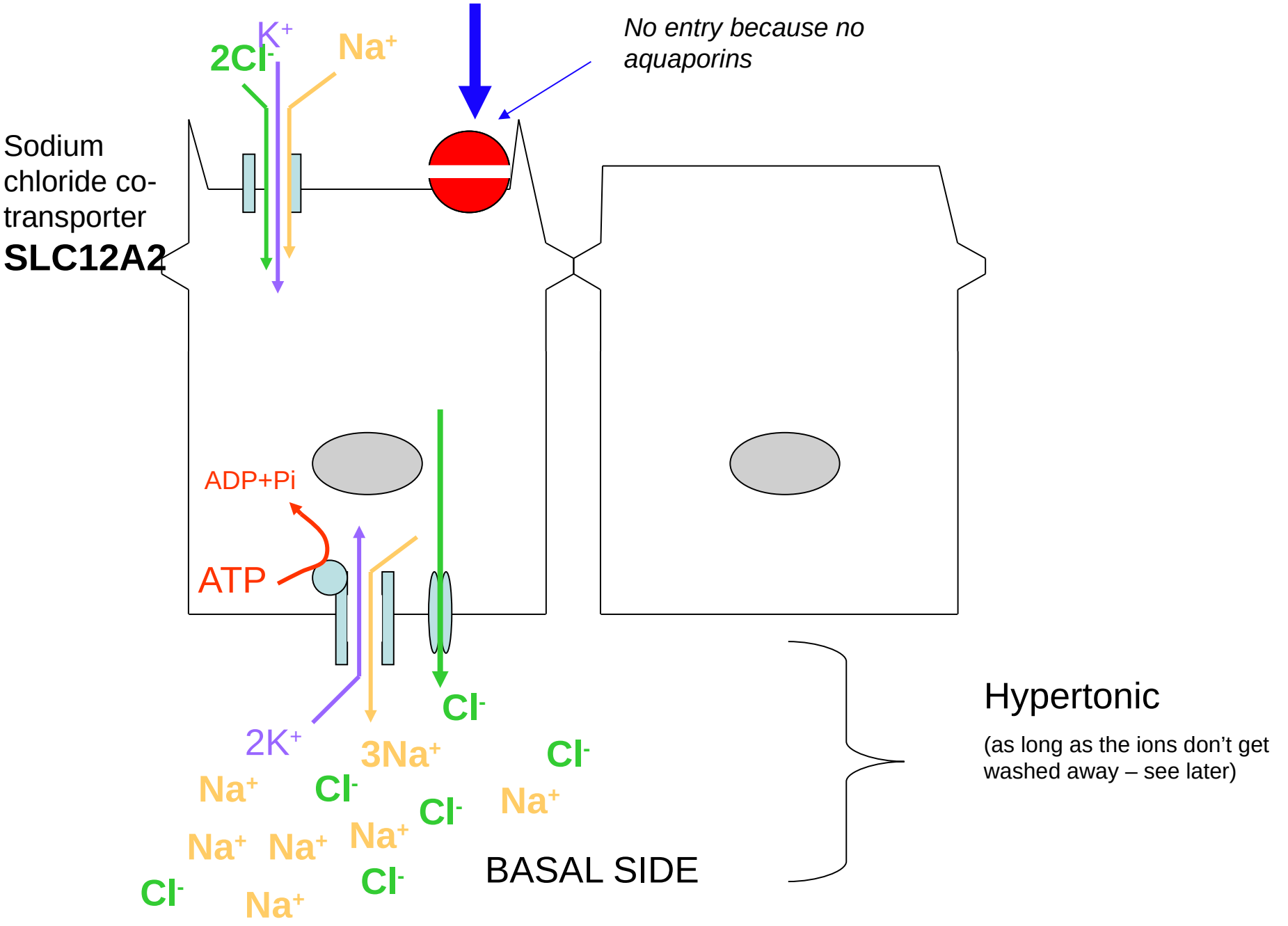
3) We have the SLCs and ion channels that can parasitize the Na^{+} gradient to move ions and small molecules about.

4)We have the fact that osmosis will make water 'follow' ions

Osmosis only takes water from a dilute solution (of solute) to a concentrated one.

…. So if we are to tempt water out of the tubule to concentrate urine, we have to provide a destination that is *more* concentrated that the urine.

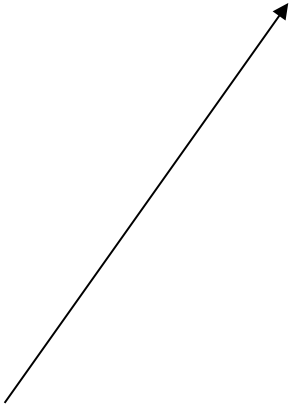
Let this run:


K+
2Cl-
Na+
No entry because no aquaporins
Sodium chloride co-transporter
SLC12A2
ADP+Pi
ATP
Cl-
2K+
3Na+
Cl-
Na+
Cl-
Cl-
Na+
Na+
Na+
Na+
Cl-
Cl-
Na+
BASAL SIDE
Hypertonic
(as long as the ions don't get washed away – see later)

OK – so we can easily make a bit of tissue just outside the tubules very hypertonic.

But we did this by *stopping* water moving.

… so we can't use it to draw water across the same cells.

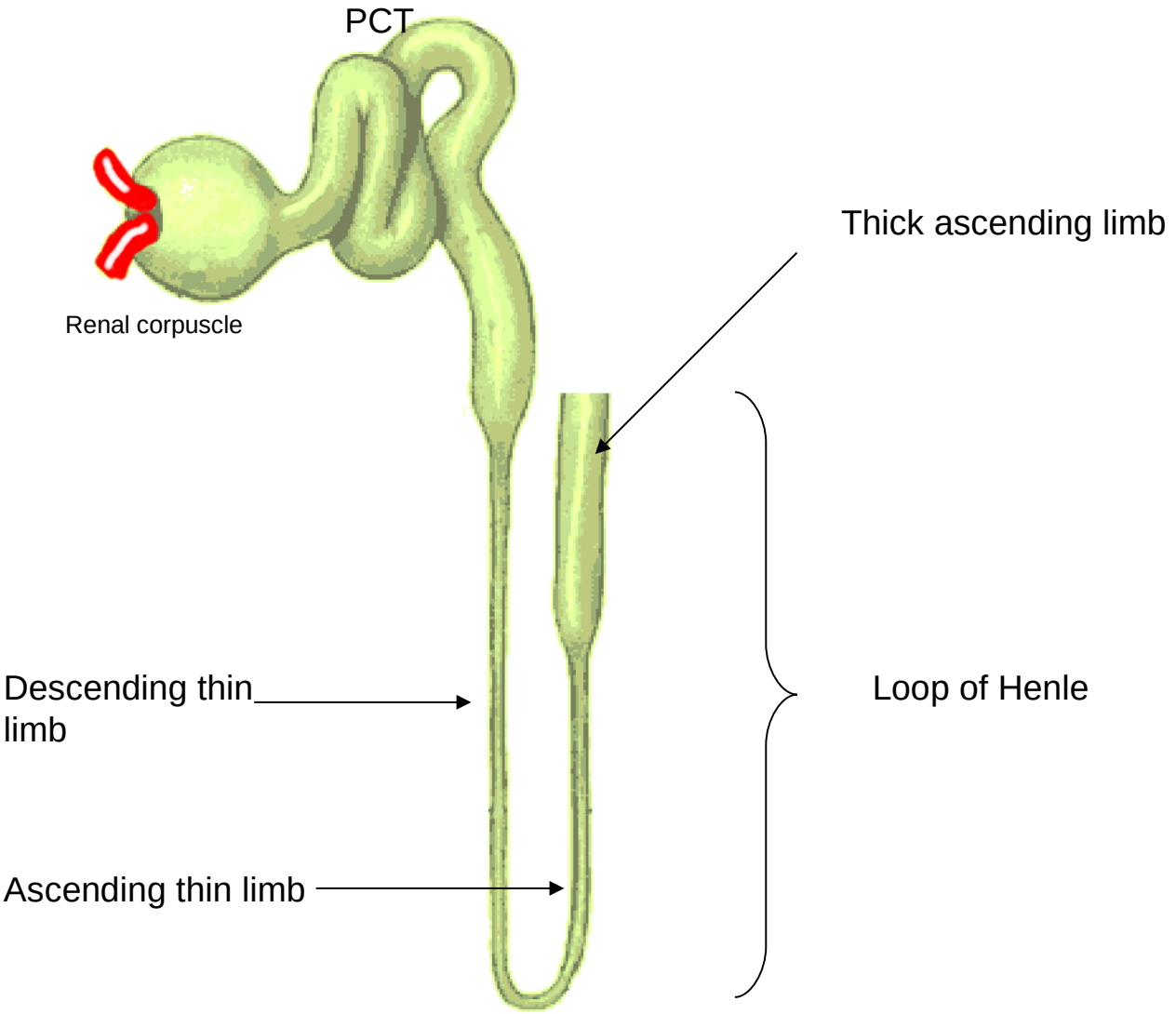


But what if we pull it across some other cells?

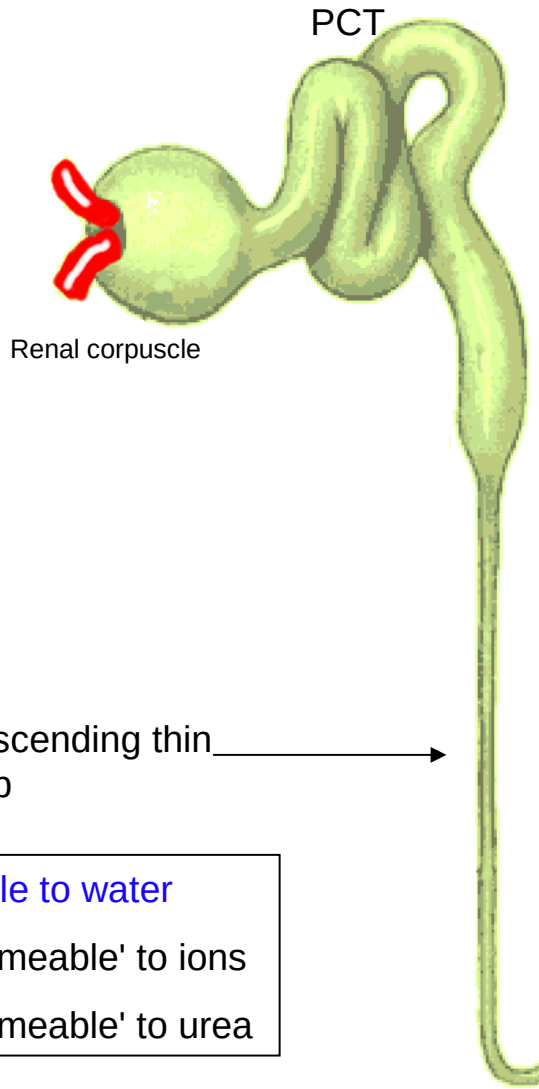
- This would take an anatomical arrangement that has two bits of tubule running in the same surrounding environment.

The Loop of Henle

Friedrich Henle



The Loop of Henle



Thick ascending limb

Active recovery of ions (driven by Na pump)

Descending thin limb

Permeable to water

'Impermeable' to ions

'Impermeable' to urea

Ascending thin limb

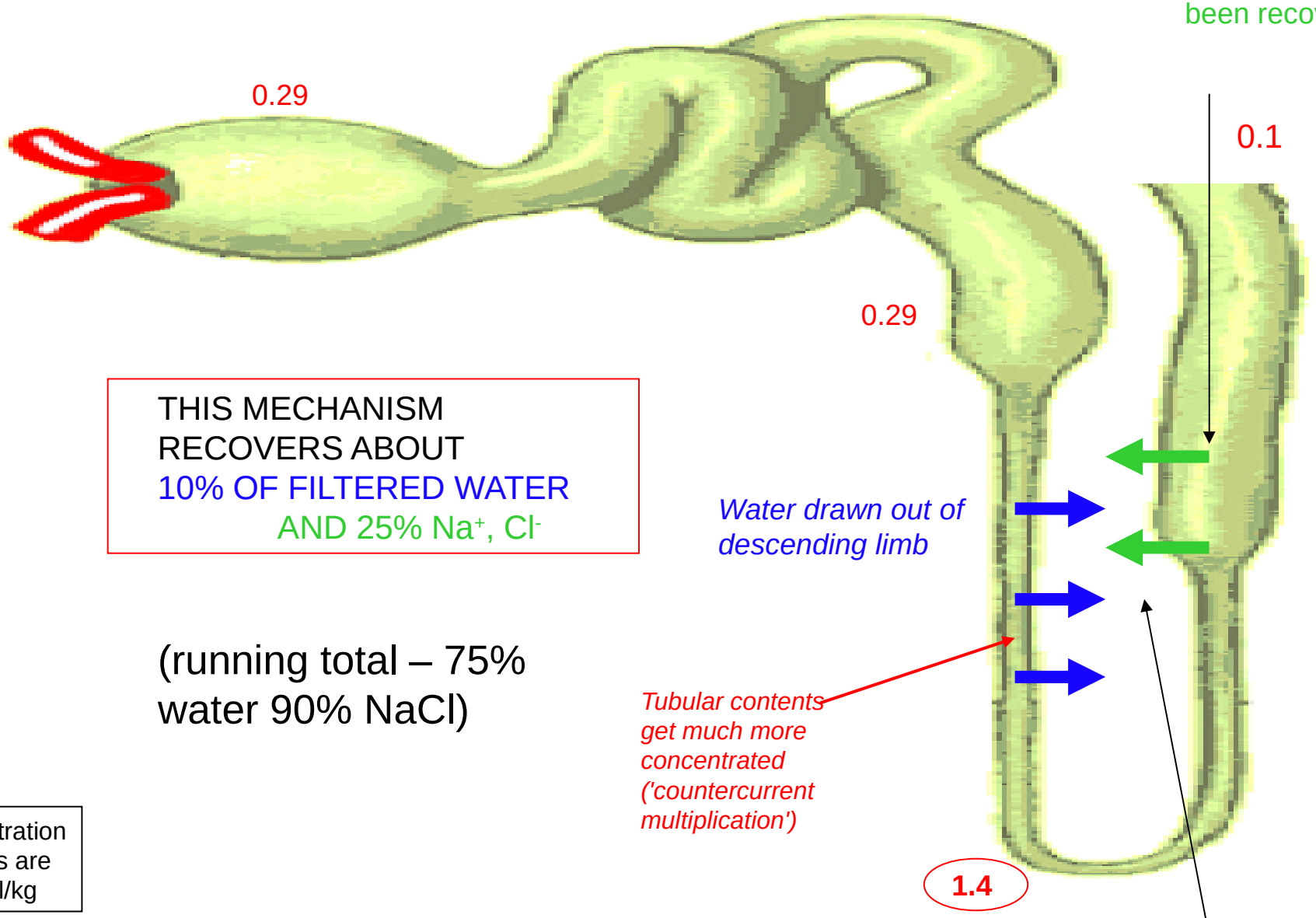
Impermeable to water

Permeable to ions

Permeable to urea

Cells in the thin descending limb have lots of aquaporins but little ion transport.

Gets more diluted (but that's mainly because so much has been recovered)



THIS MECHANISM RECOVERS ABOUT
10% OF FILTERED WATER
AND 25% Na^+, Cl^-

(running total – 75% water 90% NaCl)

Concentration numbers are in osmol/kg

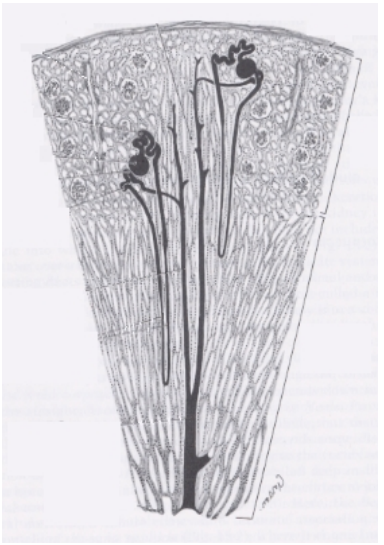
(*image has been stretched* ⟷ *for clarity of labelling*)

This recovery of water may not seem much, but view the point of the LoH is making a hypertonic zone.

We'll use that zone again in a moment, and that's when we really get the payback.

So how do we stop the high osmolarity of the Henle's loop area being washed away?

1) Anatomy (1): we have all of the loops in the same area and all of the renal corpuscles somewhere else:



0.29

Renal corpuscles all out here (cortex)

LoH down here (medulla)

1.4

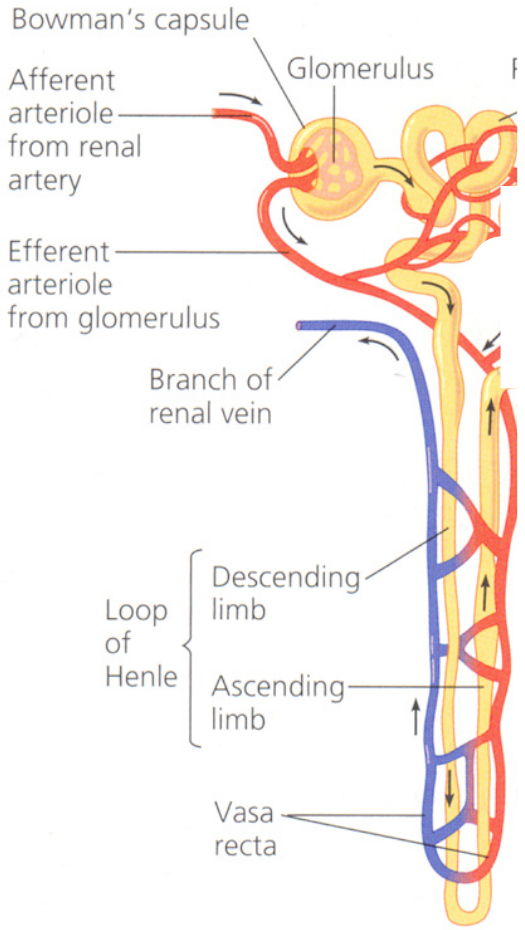
Osmolality in osmol/kg

2) Anatomy (2): we are careful with the way we organize the blood system, which would be the main transport system that could mess this up.

Problem: how do we stop out hypertonic region being swept away by blood flow in the tissues?

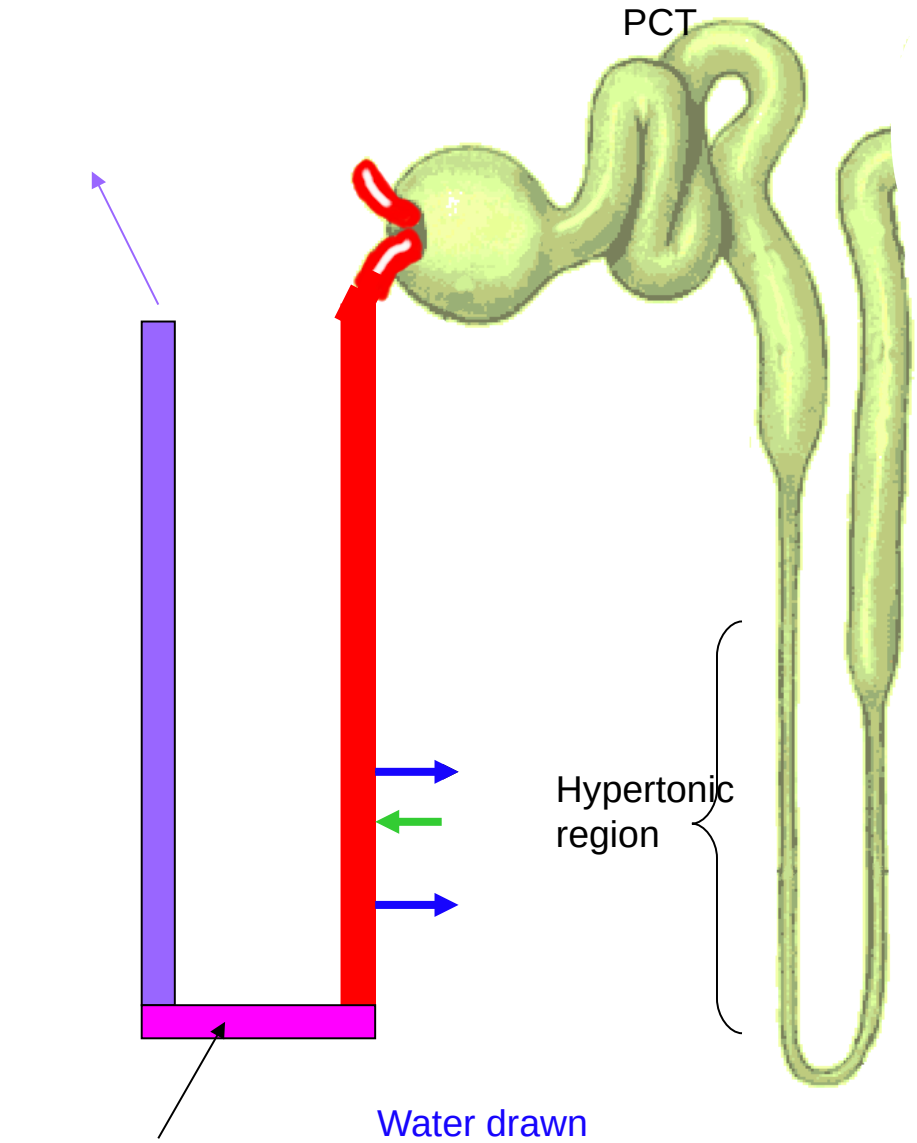
The blood vessels emerging from the glomerulus go on to form a secondary capillary system – the *vasa recta*

The important thing to see is that the blood comes in up the conc gradient and goes out the exact opposite way.

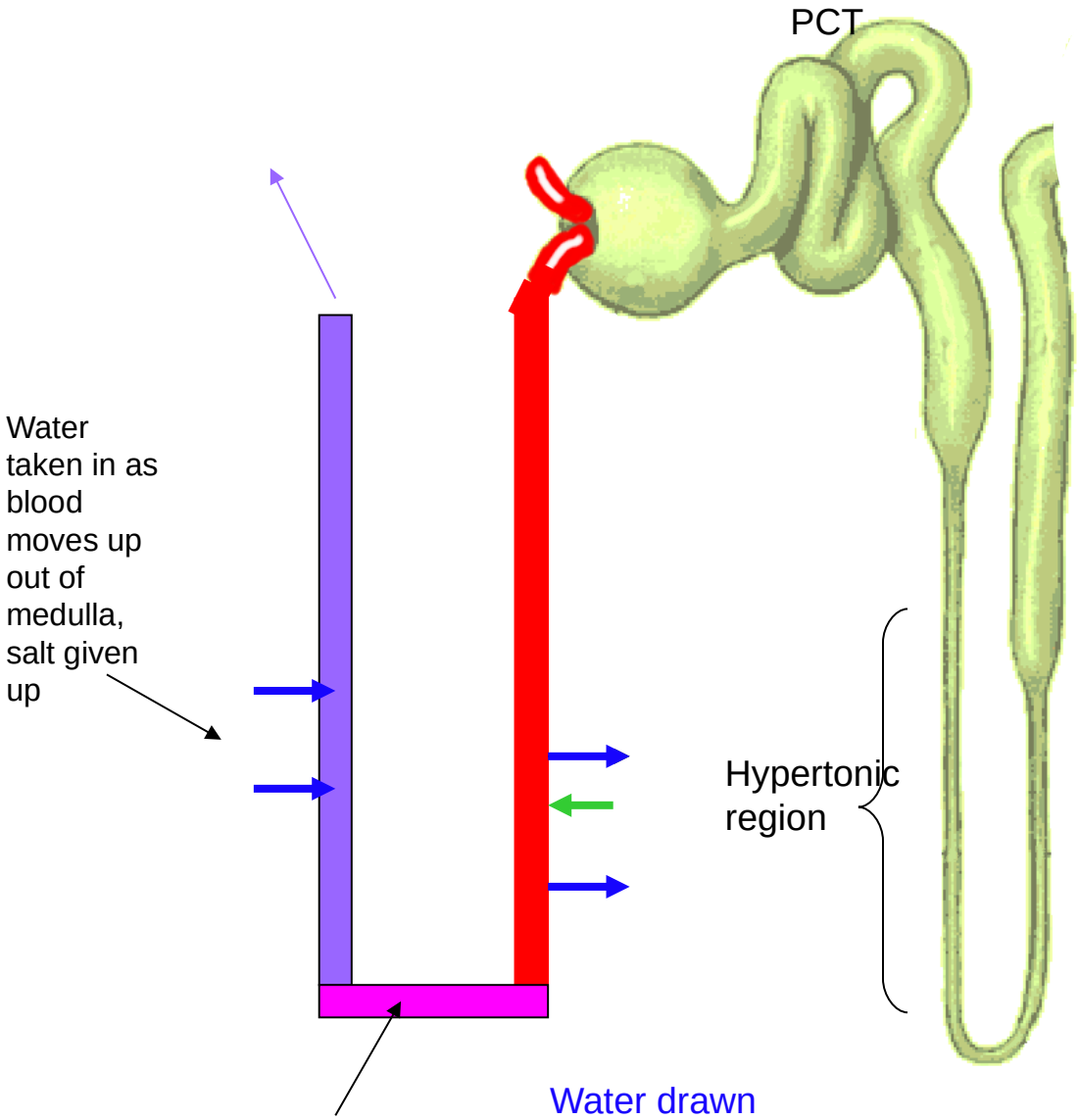


Wikipedia commons

Simplifying the anatomy:



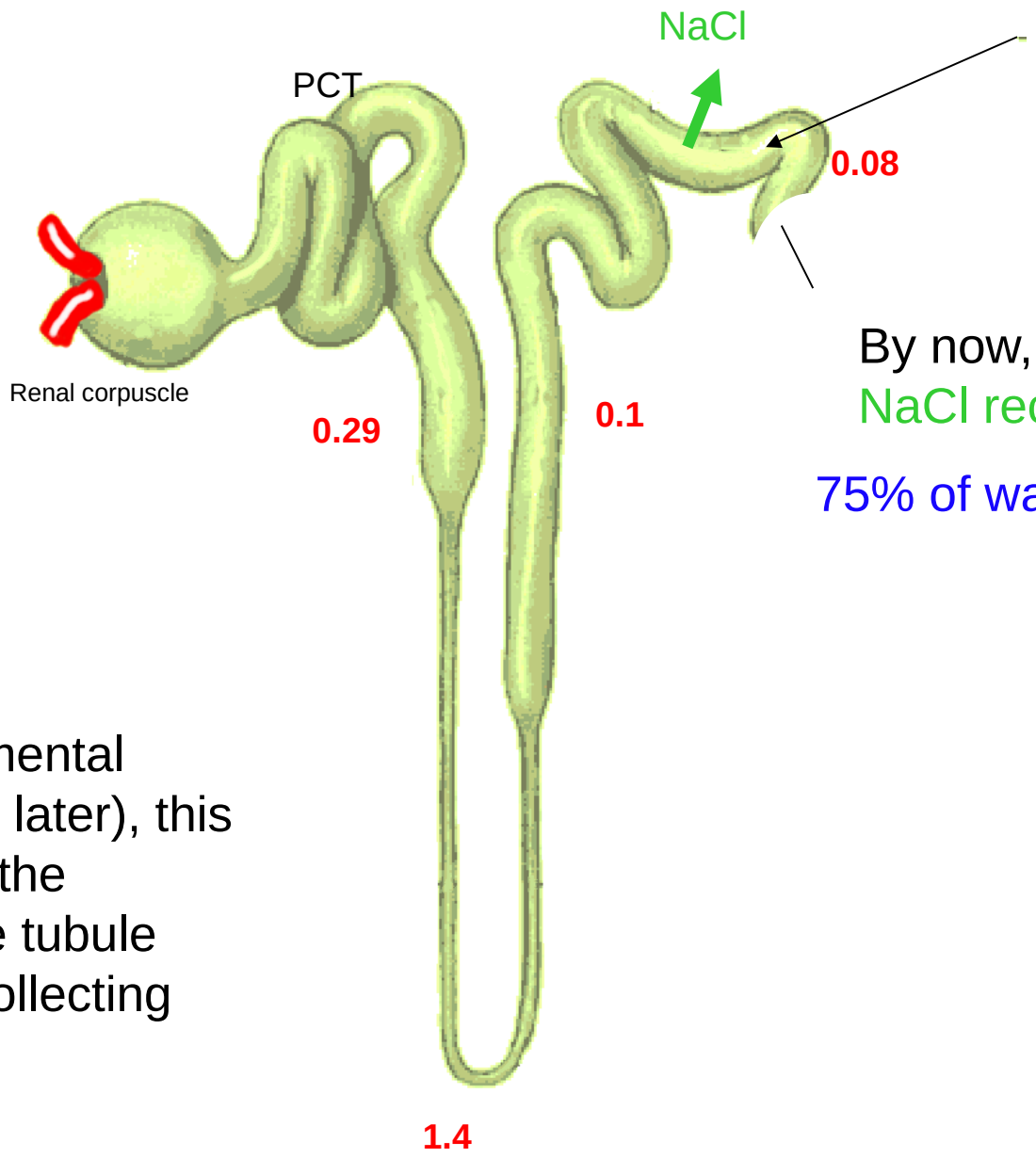
"Countercurrent exchange":



If the blood just carried on down the screen to exit, it could not draw out the water it dumped or give back ions it took

(there are still some losses of course)

The distal tubule: more recovery of ions. No water transport.



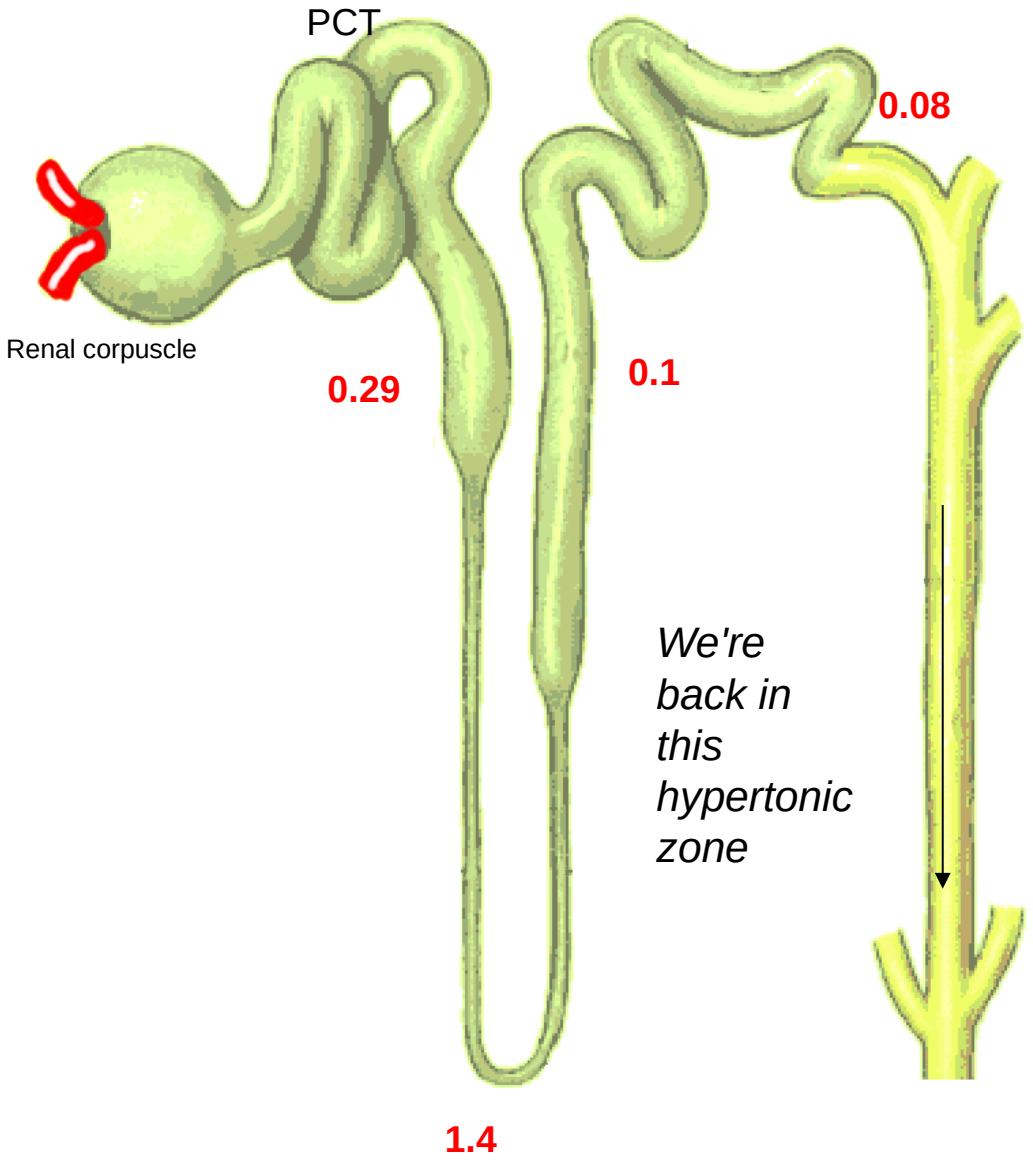
By now, 95% of NaCl recovered.

75% of water

For developmental reasons (see later), this is the end of the nephron. The tubule joins into a collecting duct system.

NB: this nephron has been 'spread out' – the Distal Tubule will really come close to the corpuscle again

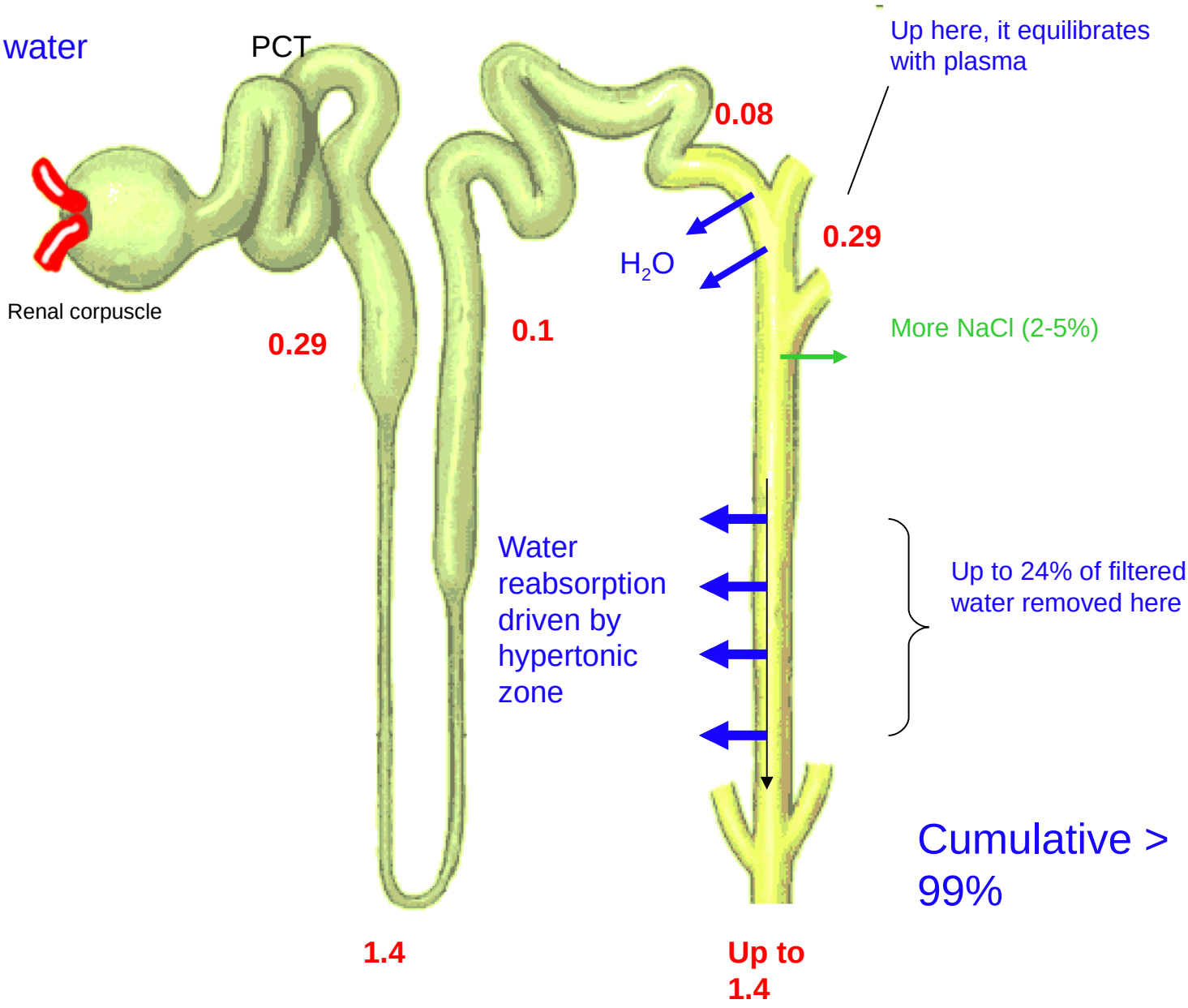
The collecting duct



NB: this nephron has been 'spread out' – the Distal Tubule will really come close to the corpuscle again

The collecting duct:

regulated permeability to water



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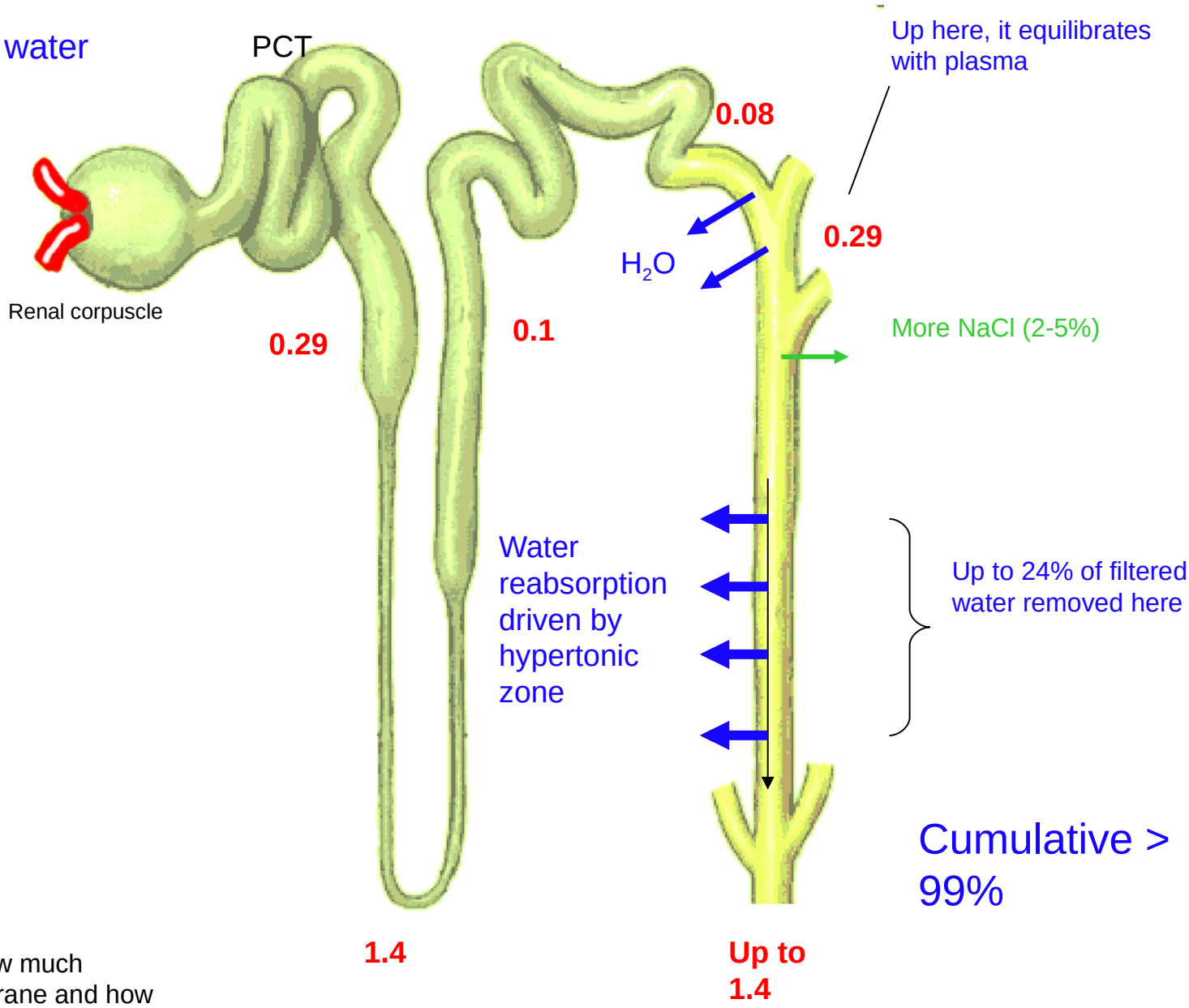
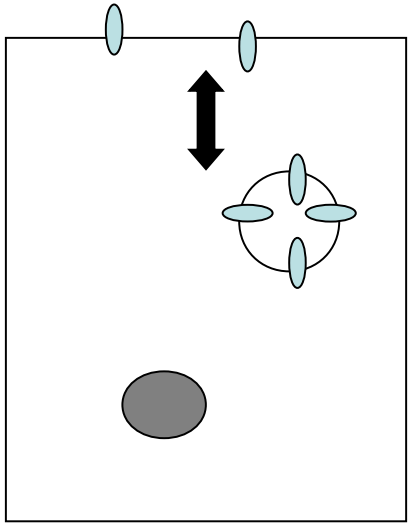
regulated permeability to water



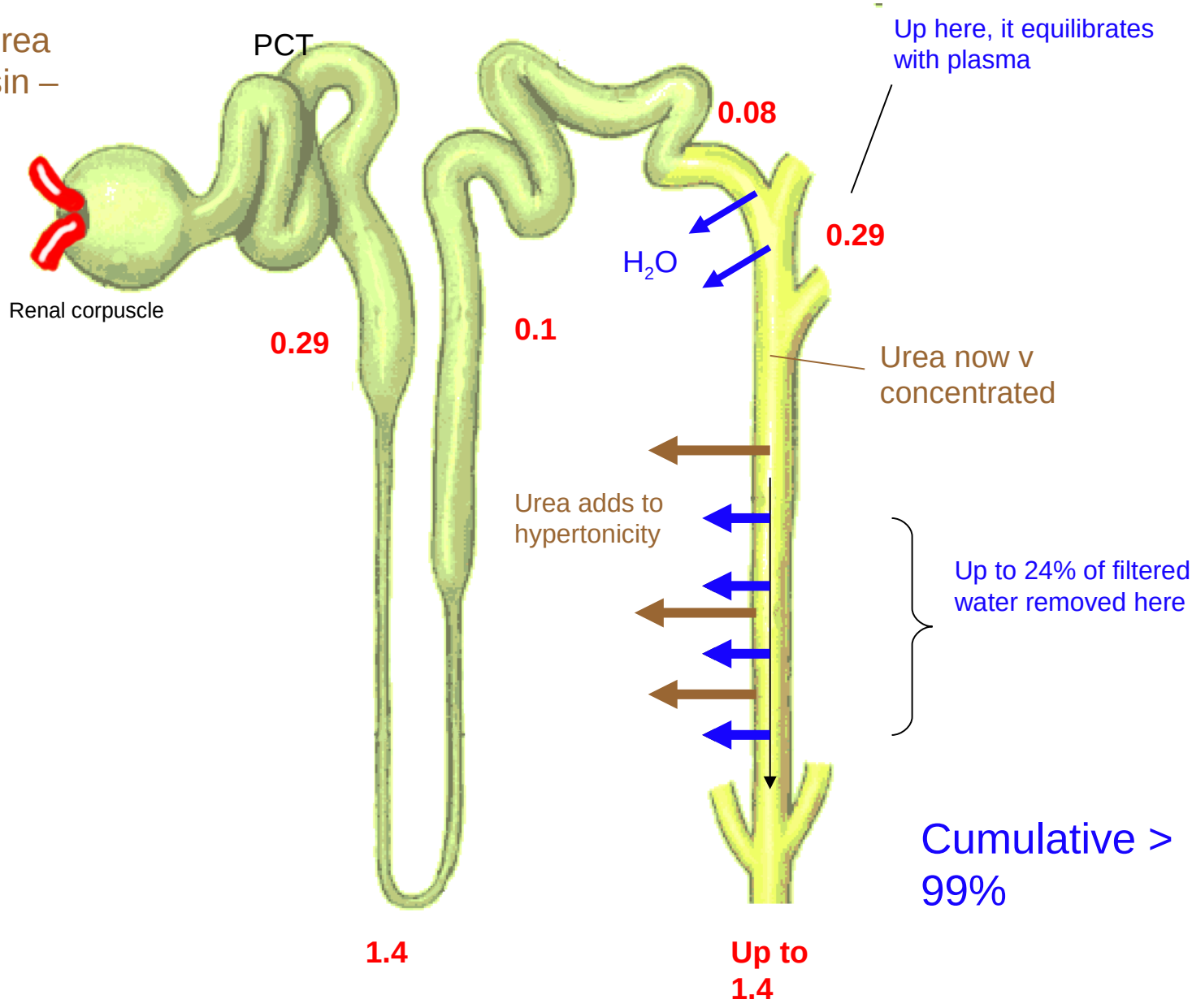


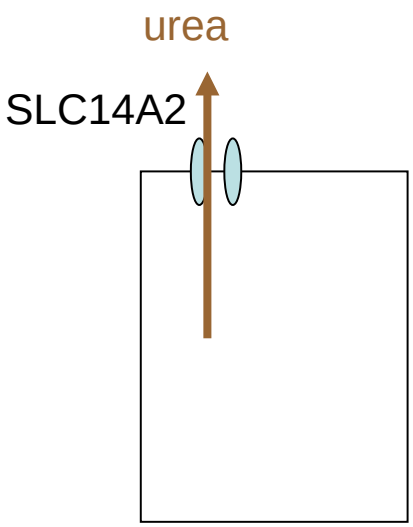
Coll duct cells can choose how much aquaporin to put in the membrane and how much to store on vacuoles. Regulated by vasopressin (see lecture 4)

NB: this nephron has been 'spread out' – the Distal Tubule will really come close to the corpuscle again

The collecting duct:

The duct can choose to leak urea (again regulated by vasopressin – see lecture 4)





NB: this nephron has been 'spread out' – the Distal Tubule will really come close to the corpuscle again

Please note: I have given you the accepted 'text-book' explanation, but there are uncomfortable pieces of data that challenge it. This is good review:

Layton AT, Layton HE. (2011) Countercurrent multiplication may not explain the axial osmolality gradient in the outer medulla of the rat kidney. Am J Physiol Renal Physiol. 2011 Nov;301(5):F1047-56

I suspect that the story I told you will be modified in its detail, but the core will remain.

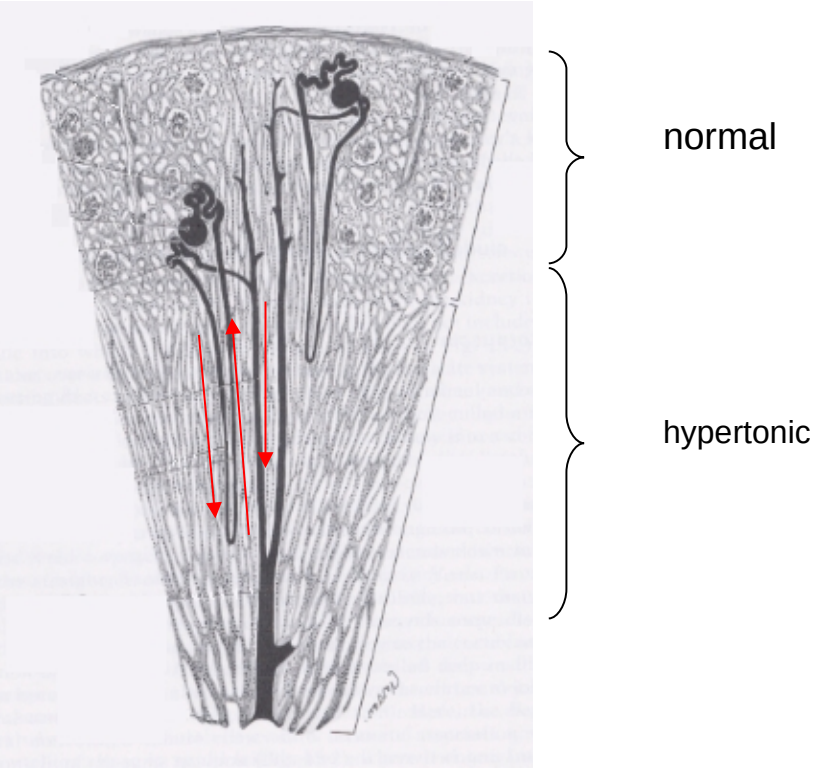
As year 2 medical students, you do not have to engage with this debate – I am just flagging it in case you come across it and get confused.

Summary so far:

- The loop of Henle makes the medulla very hypertonic
- This draws water from tubules that pass through there – especially collecting duct.
- The duct can help by letting some urea into this area

This function depends on a specific anatomical arrangement

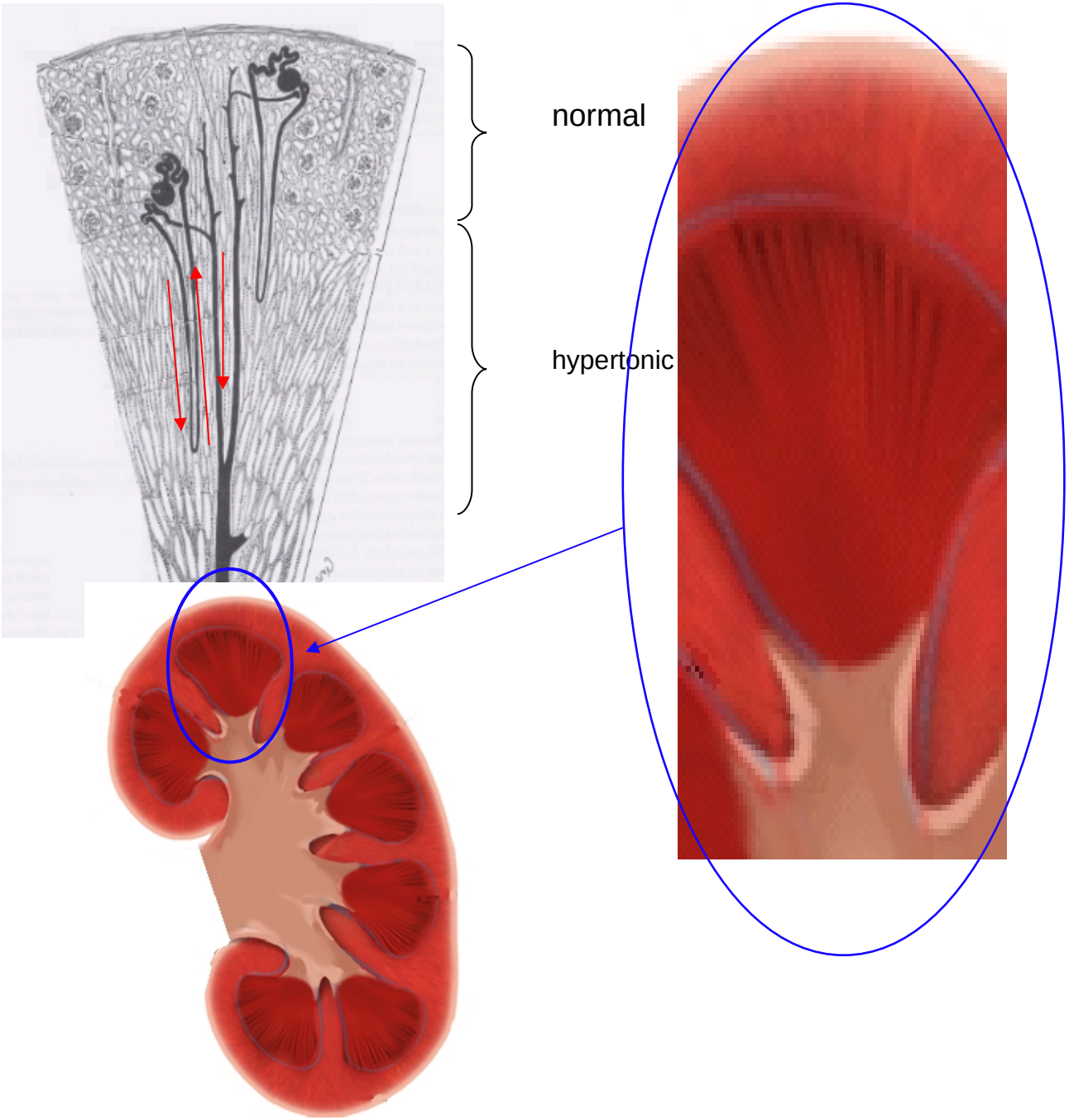
1) We need a separation between normal and hypertonic zones
2) We need the route to pass again through the hypertonic route



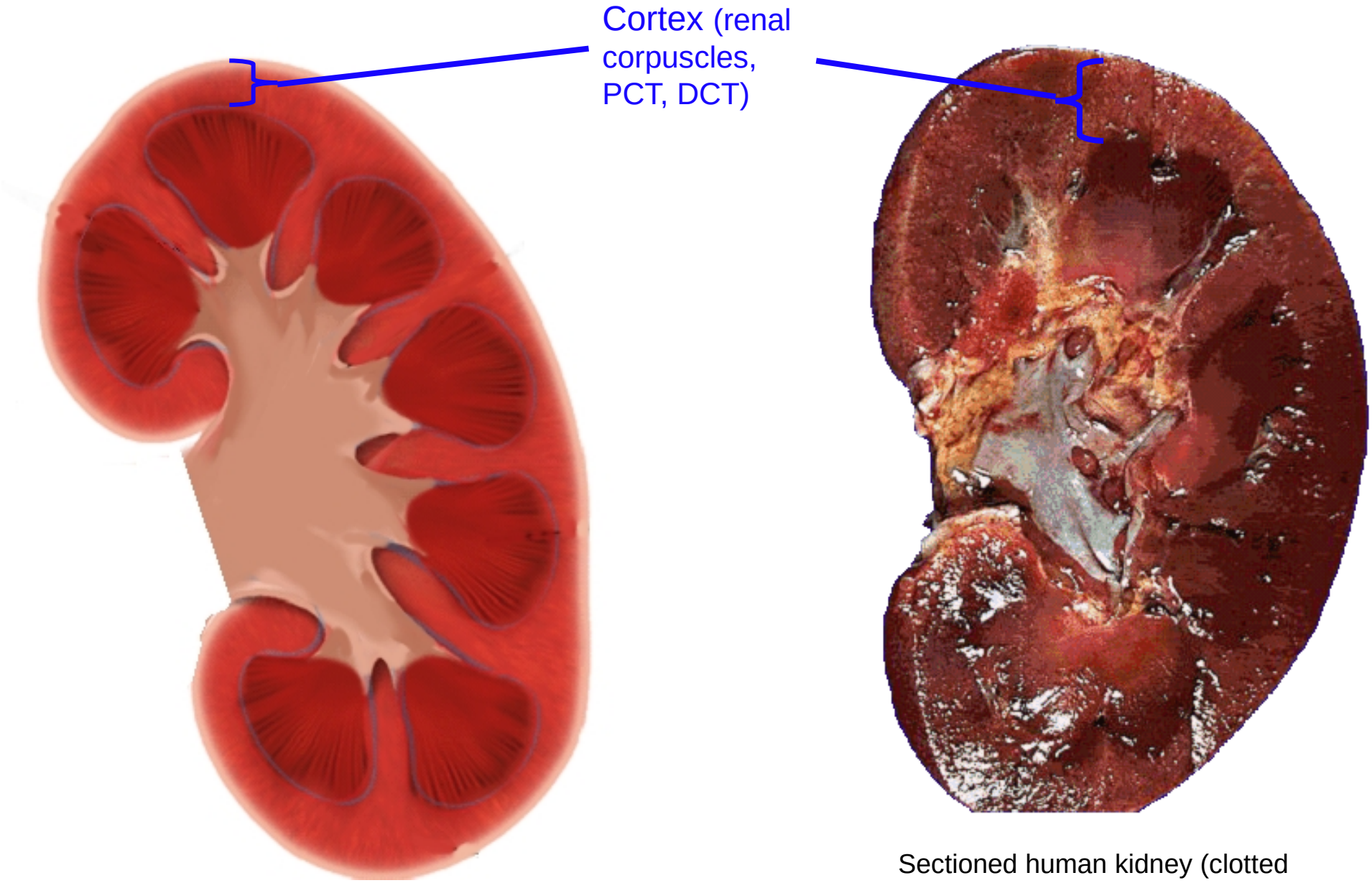
(you saw this picture in the last lecture)

This function depends on a specific anatomical arrangement

1) We need a separation between normal and hypertonic zones
2) We need the route to pass again through the hypertonic route
3) So it makes sense to have the normal zone on the outside of the organ and the hypertonic zone near the place that urine will collect:
4) And, for a big animal like a human, to group several of these units around a central urine collecting place:

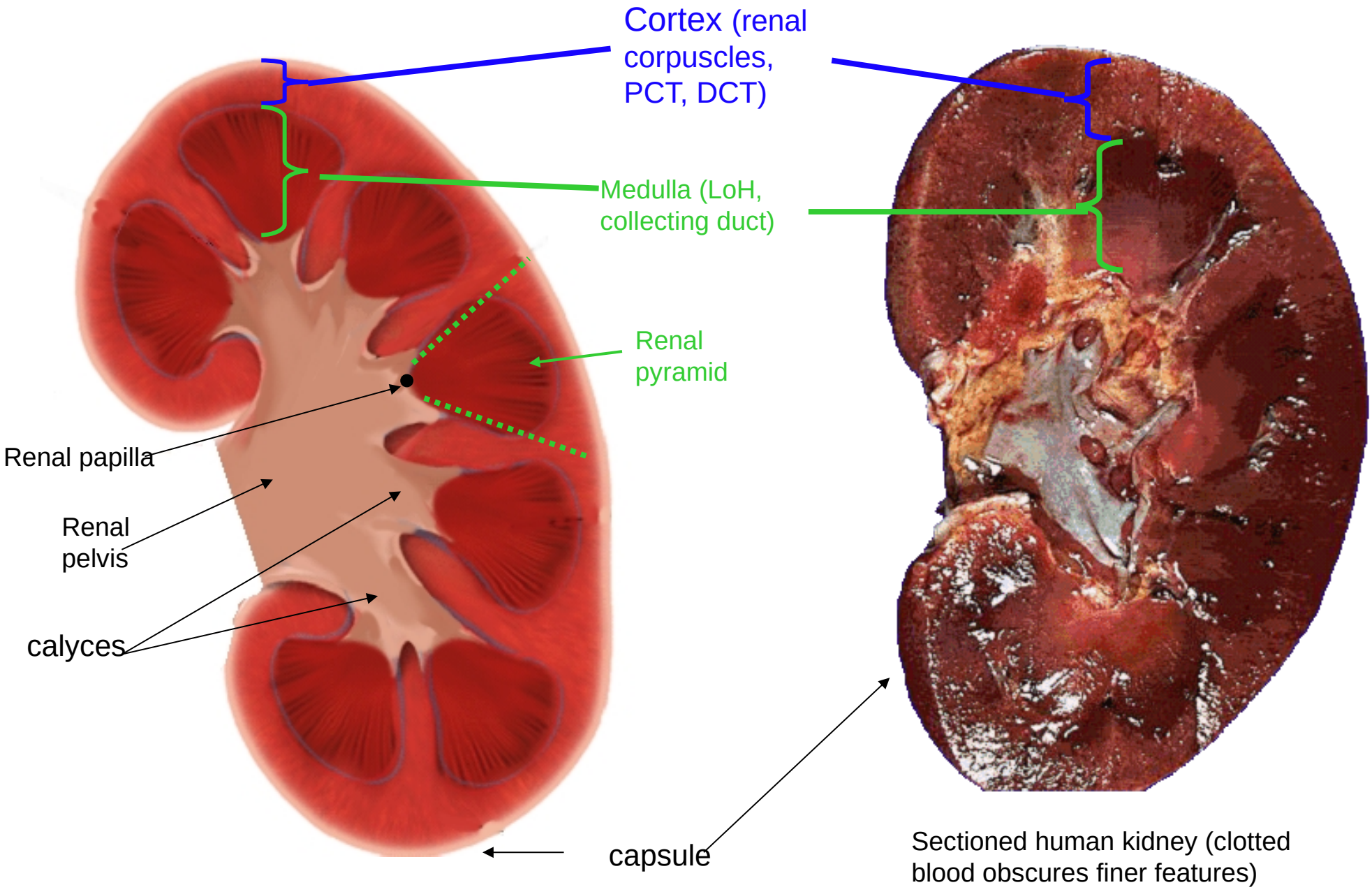


In more detail: (with some names)



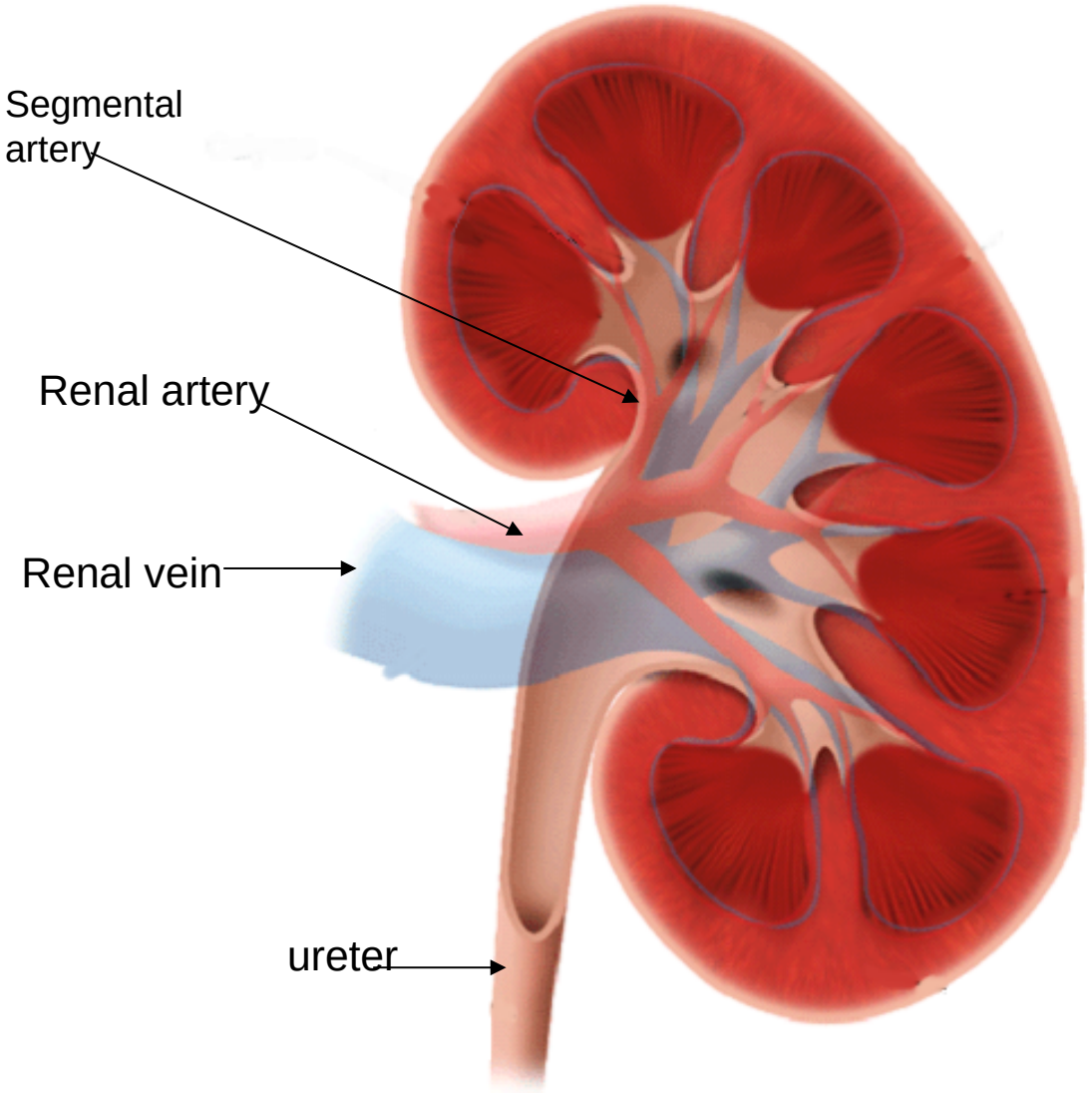
Sectioned human kidney (clotted blood obscures finer features)

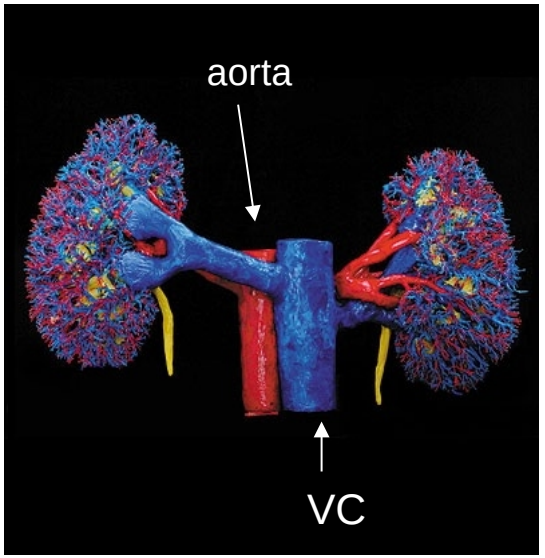
In more detail: (with some names)



Sectioned human kidney (clotted blood obscures finer features)

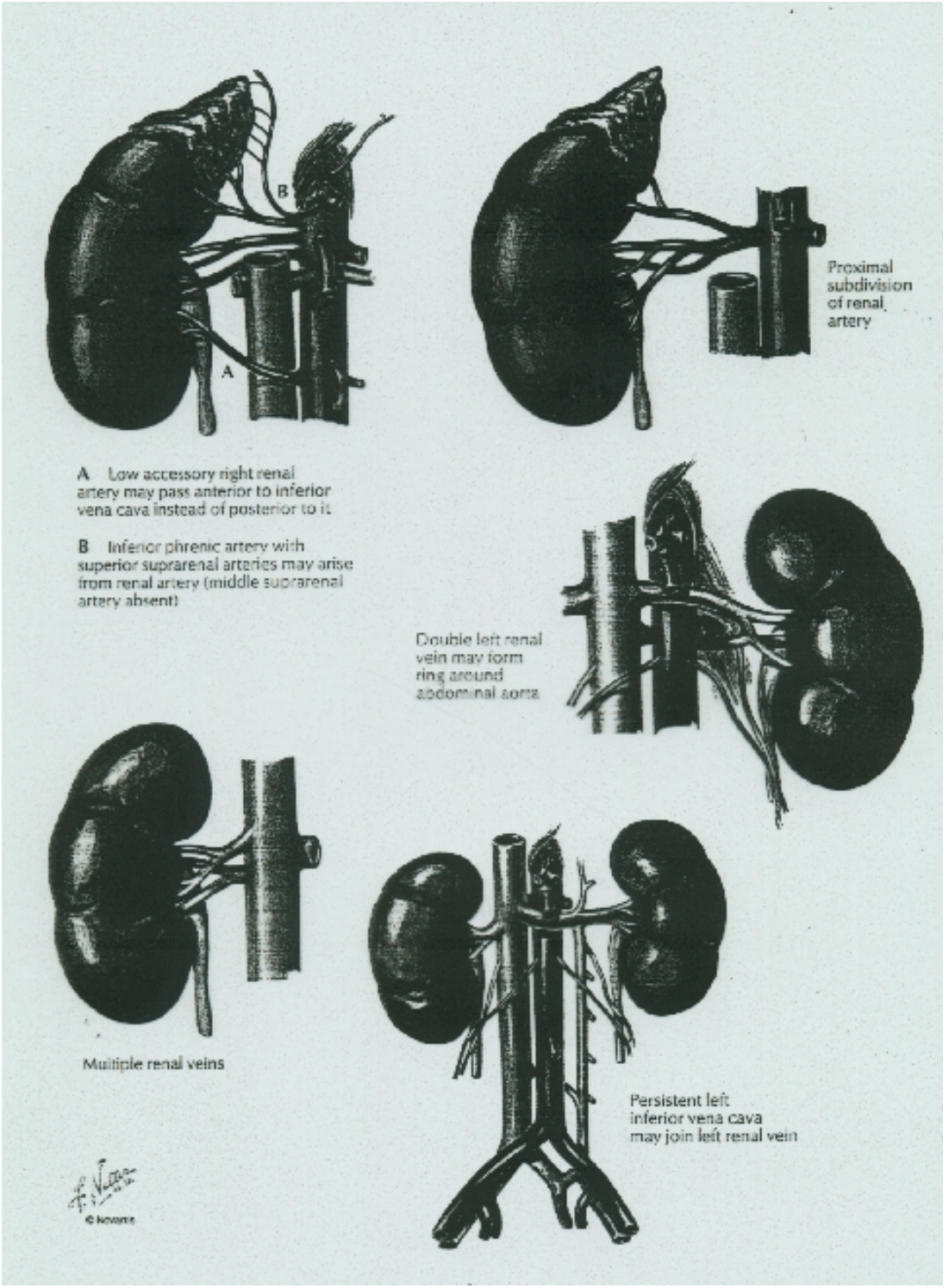
Given that the collecting duct system is a branched system that radiates from the pelvis, if makes sense for the blood system to follow the same pattern:





(you saw this in lecture 1)

There is substantial variation between individuals:



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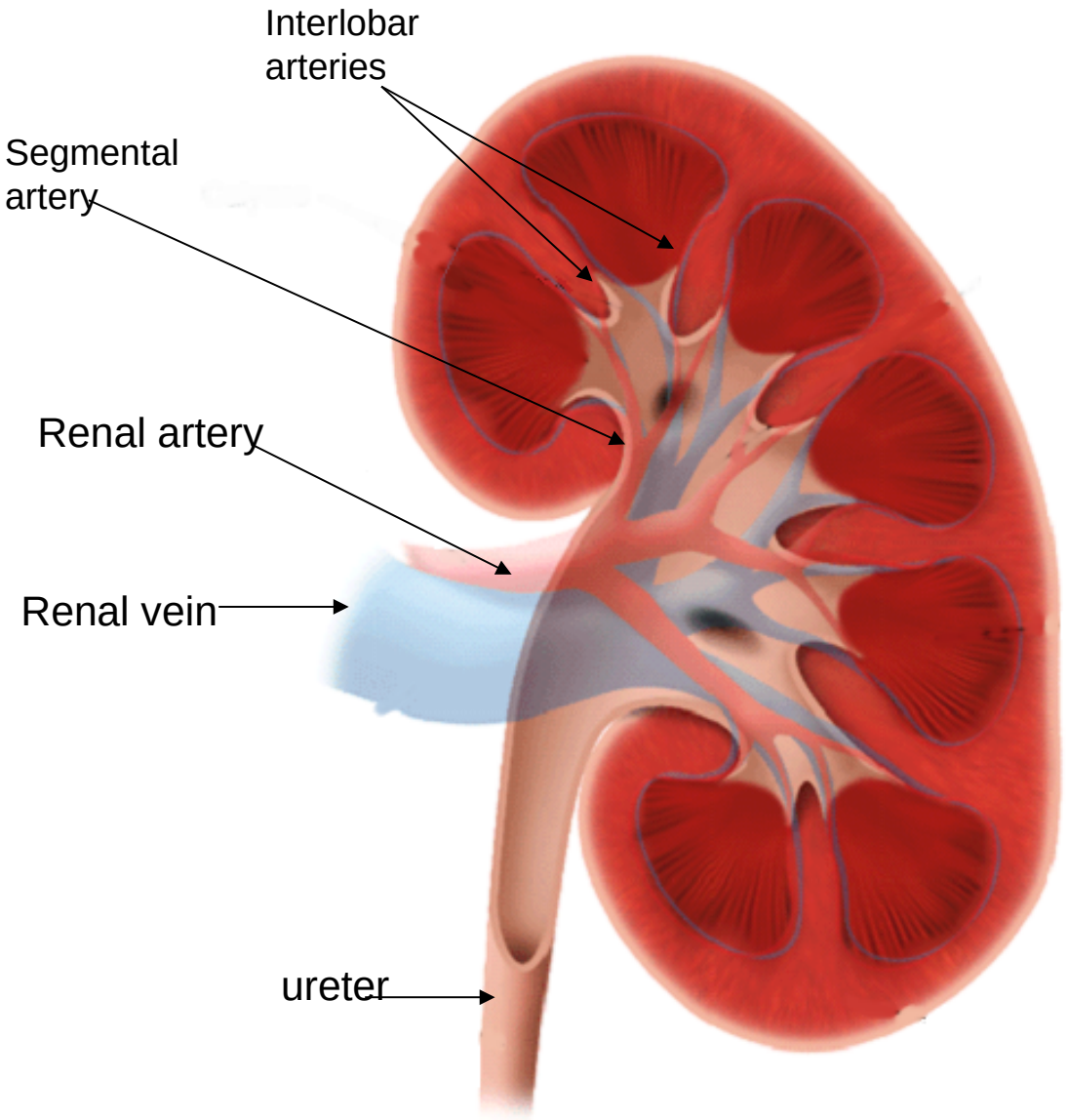
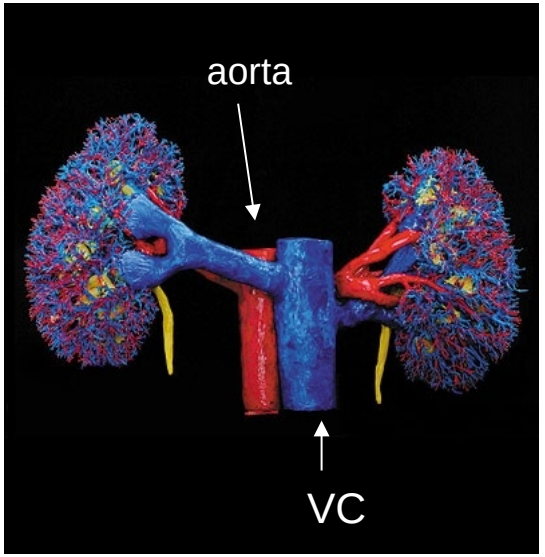




(you saw this in lecture 1)

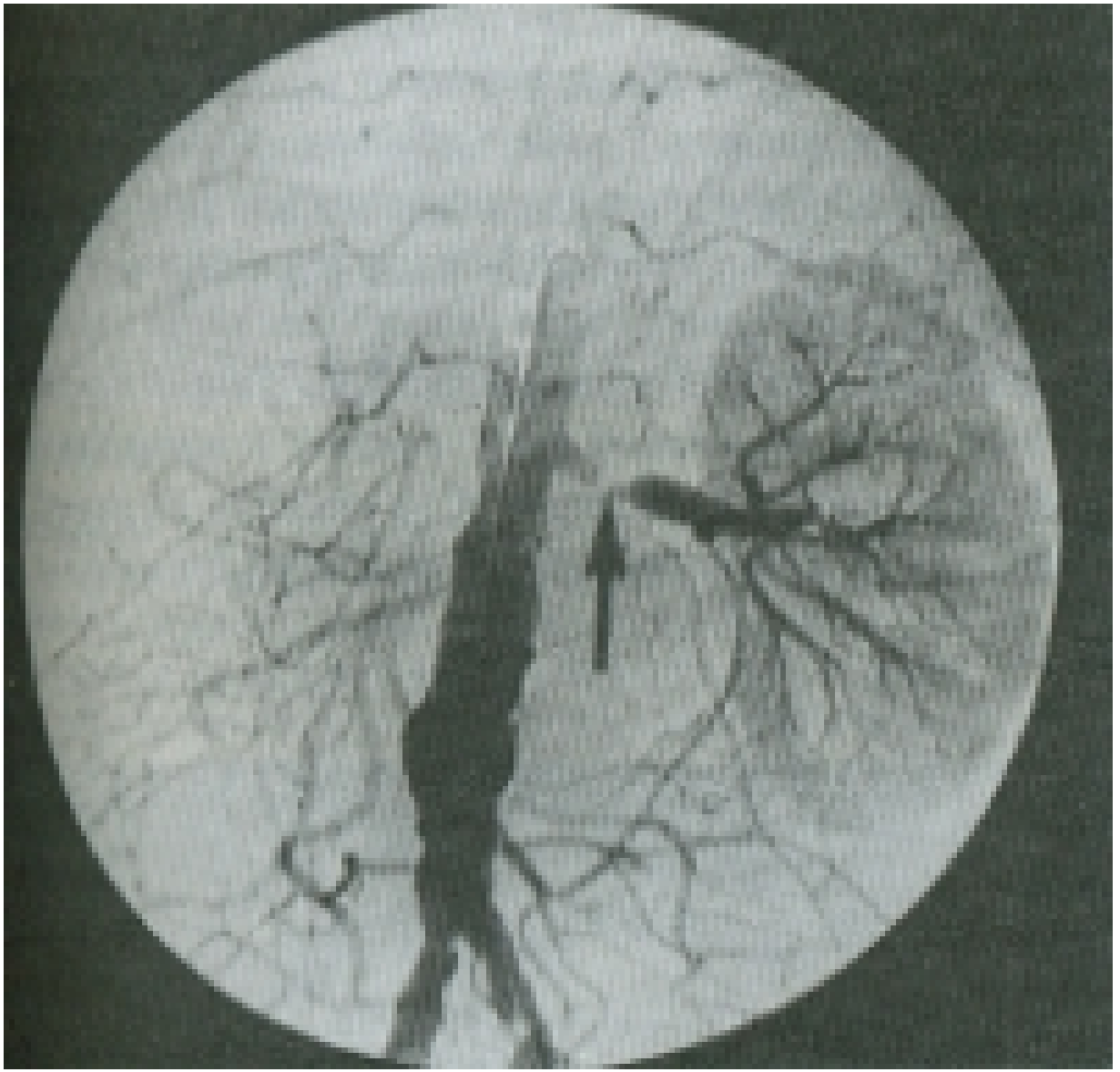
Renal arteriogram;

Left renal artery shows stenosis (narrowing by damage and scarring) - see arrow.

Right renal artery absent.

Aorta irregular and atheromatous.

{Image obtained by injecting contrast material and X-raying)

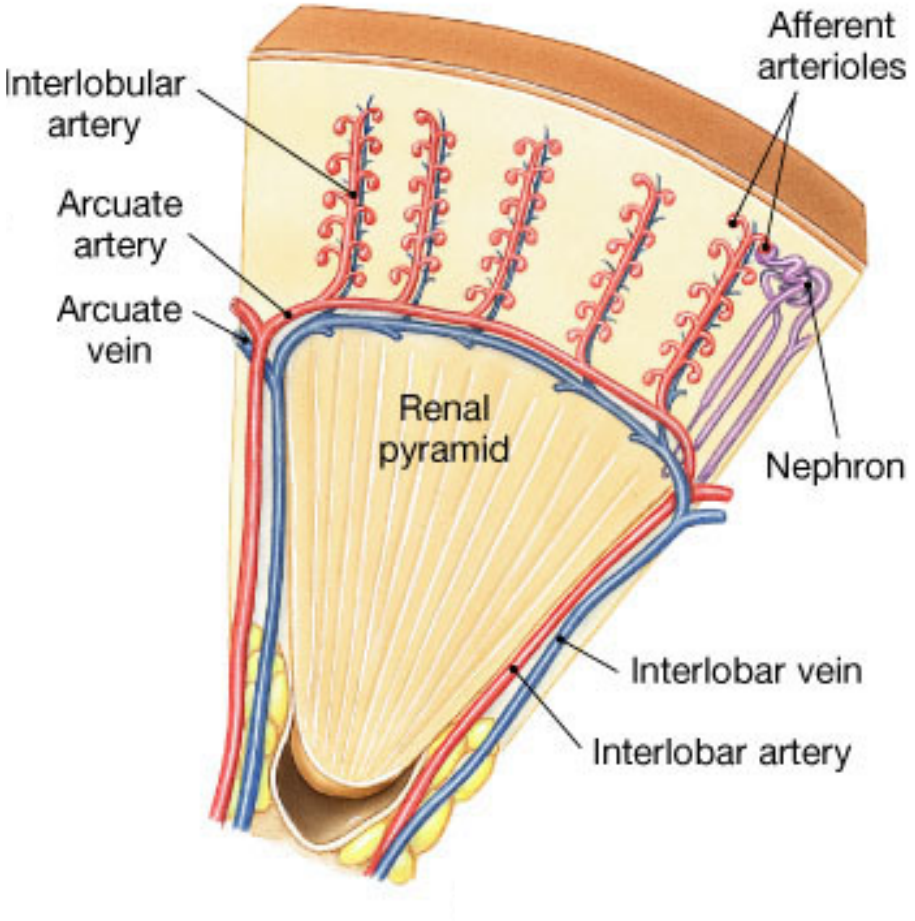


The finer vessels:

IMPORTANT:

The long runs of parallel arteries/ arterioles and veins/venules mean that there is countercurrent exchange of oxygen, so that much gets shunted from artery to vein before the blood enters capillaries.

This is probably maladaptive (a 'bug' in the machine) and it means that kidneys are particularly sensitive to ischaemia.

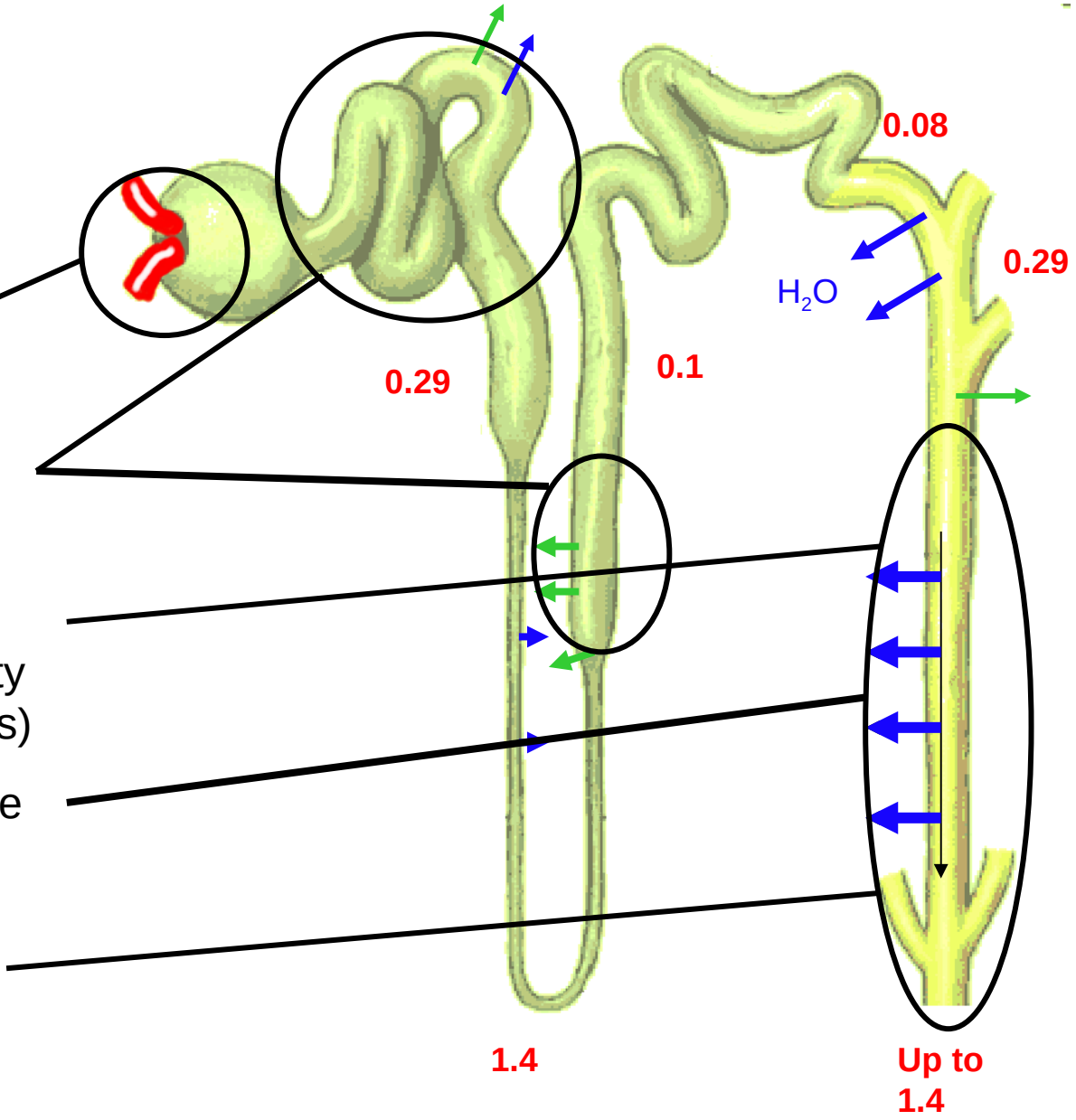


Low renal oxygen -> erythropoietin release -> more red cells made in bone marrow

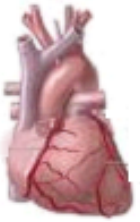
Back to function: How is this lot all controlled?

Things that can be altered:

1) Blood flow to glomerulus:
2) Na^+ recovery (SLC9A3)
3) Urea recovery by CD (SLC14A2)
4) Water permeability of CD (aquaporins)
5) Acid-base balance in CD



Blood flow



There are 3 controls:

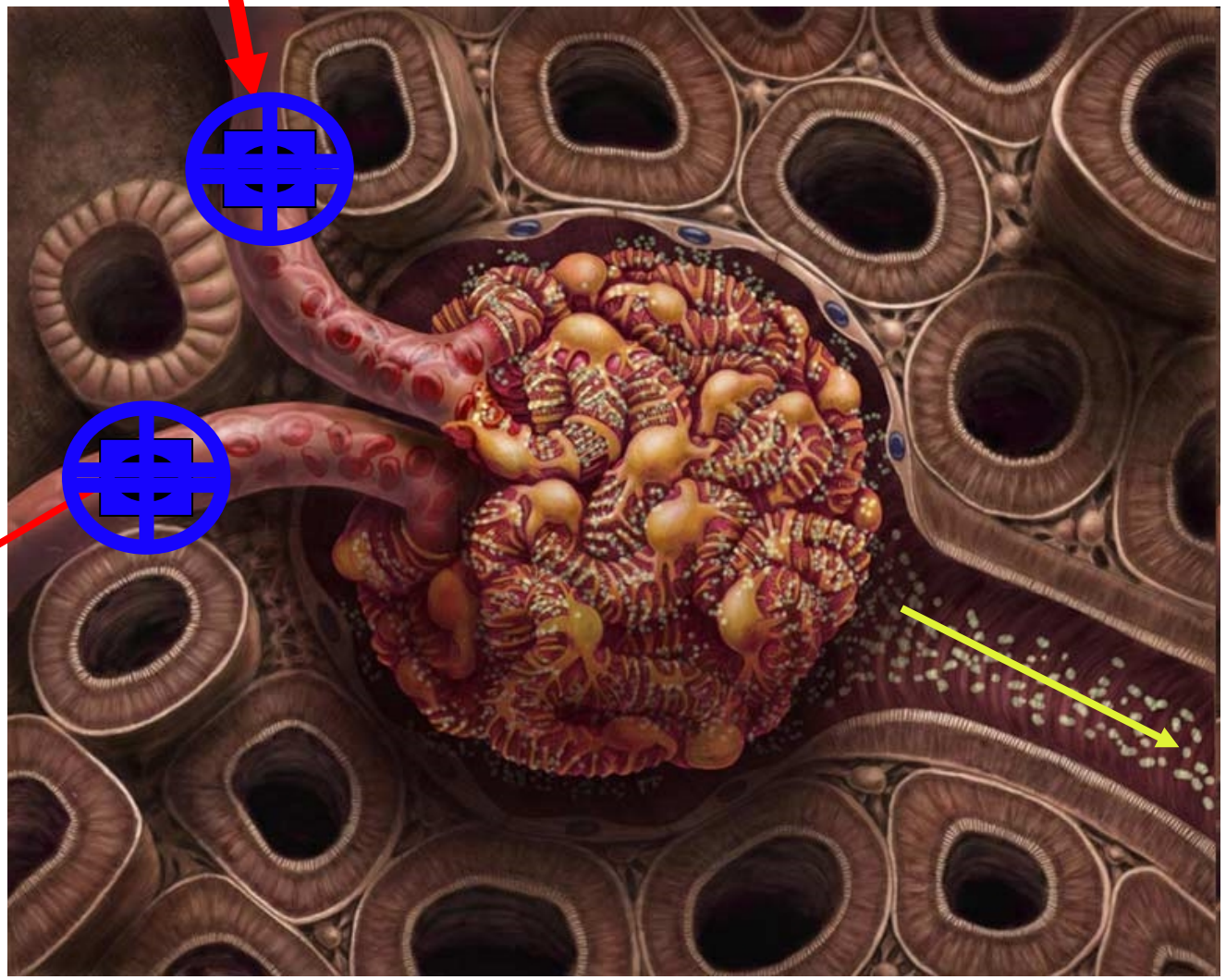
1) Systemic blood pressure

2) Constriction of afferent arterioles

Lowers glom pressure

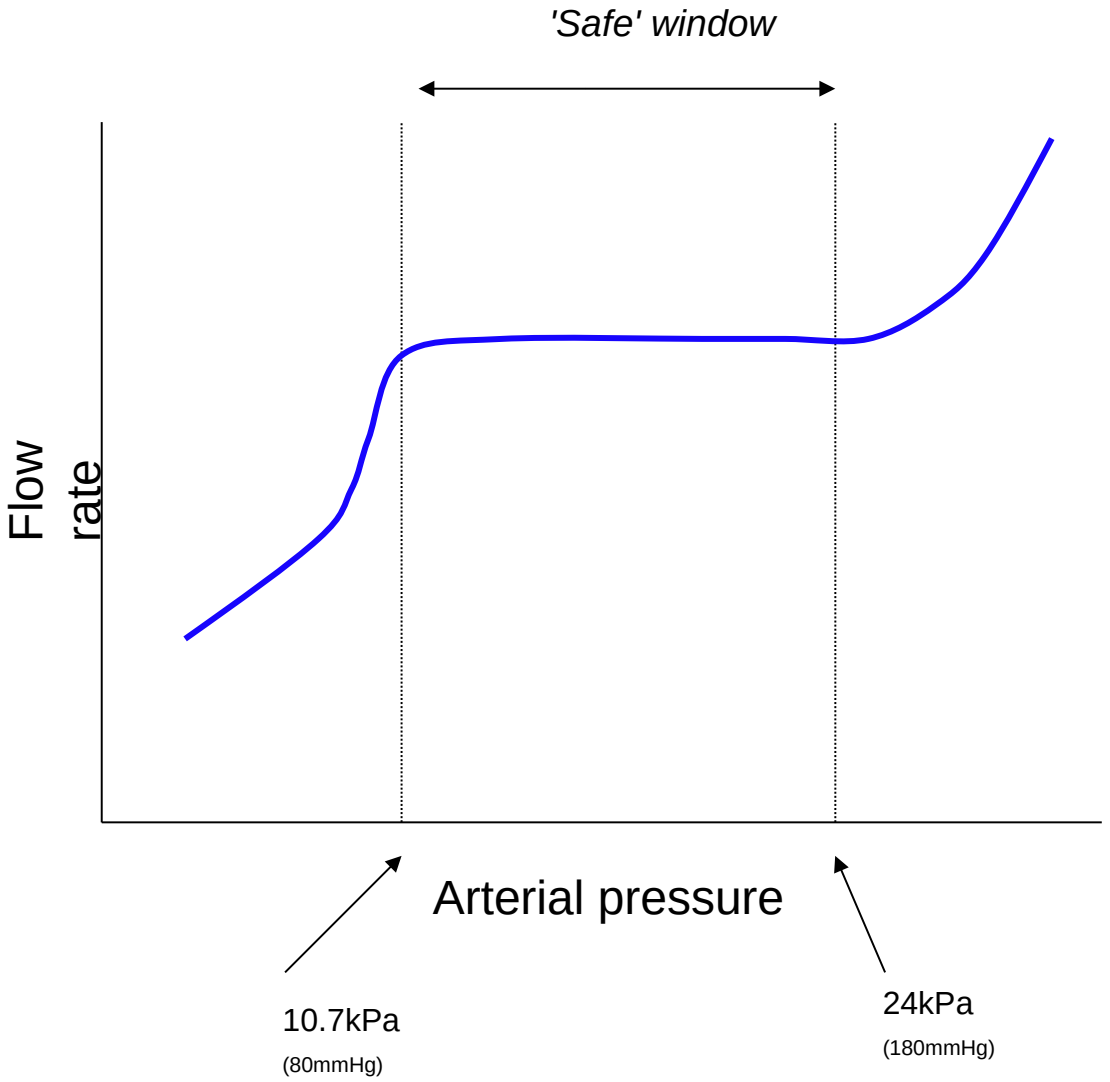
3) Constriction of efferent arterioles

Raises glom pressure



NB – diabetic changes in vessels can cause this too

Within limits, kidneys hold a constant flow rate across a range of arterial pressures;



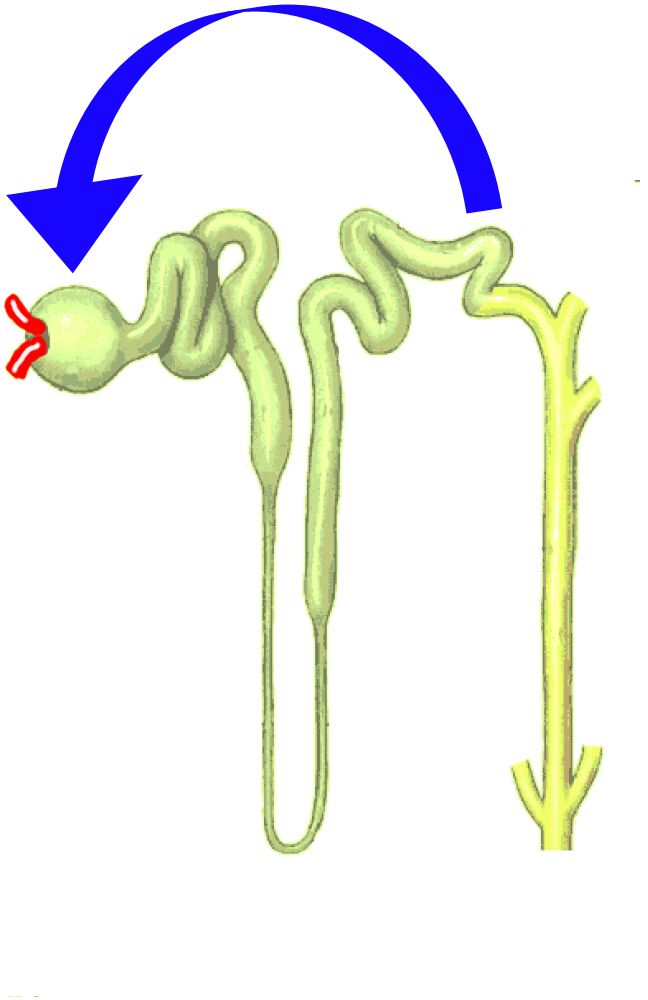
Mechanisms:

1) Direct pressure sensing in the afferent arteriole – the *myogenic mechanism*.

(stretch activated cation channels depolarize membrane and cause smooth muscle to contract: fast and protective against acute surges)

Problem:

We need this control to be nephron-by-nephron, not global, so we can't have a signal diffusing long distances.



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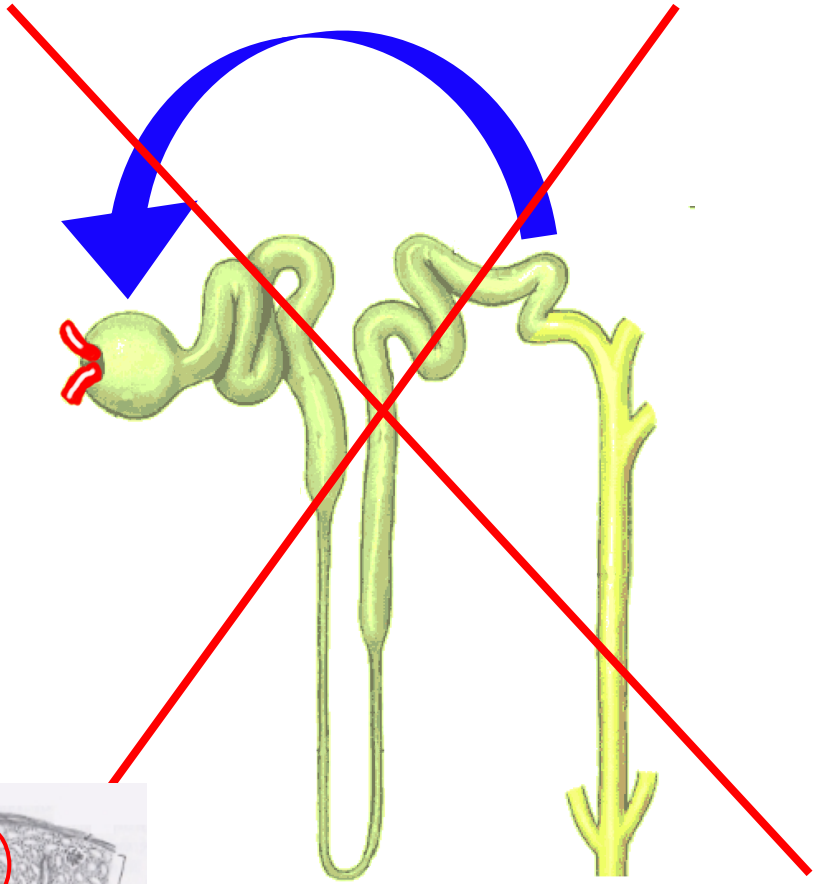
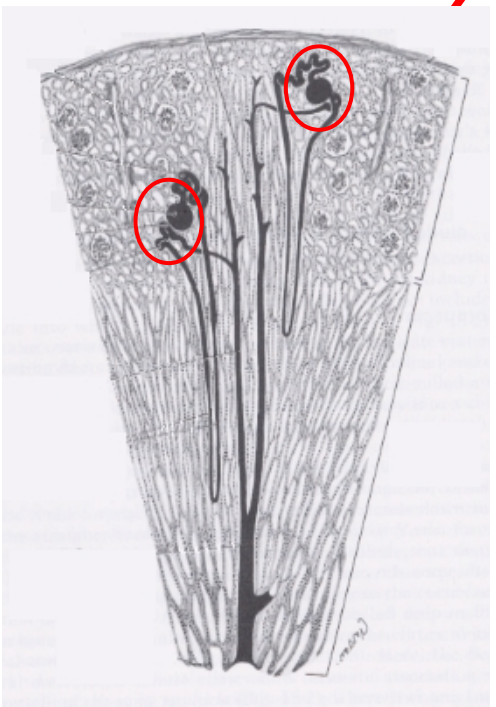
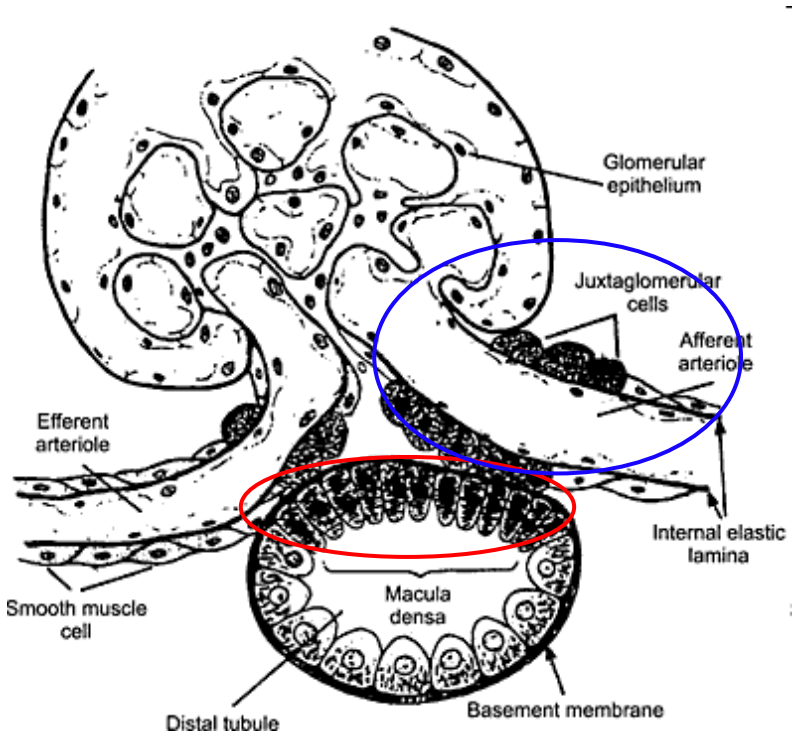


Solution:

Arrange a nephron so that the end of the distal tubule makes 'kissing contact' with the arterioles entering the glomerulus



A special zone of the distal tubule, called the *macula densa*, forms where contact is made:



Source: Kaul, C.L., Ramarao, P. (2000) Renin release and the sympathetic nervous system. Drugs Today 2000, 36(10): 699

How does the macula densa work?

Elevated glom blood pressure

Filtrate flows faster

Less time for solute recovery

More NaCl remains in the distal tubule

Macula densa cells pump out more NaCl than they usually can

(because there is more available)

Juxtaglomerular cells release adenosine

Afferent arteriole constricts in response to adenosine