by:
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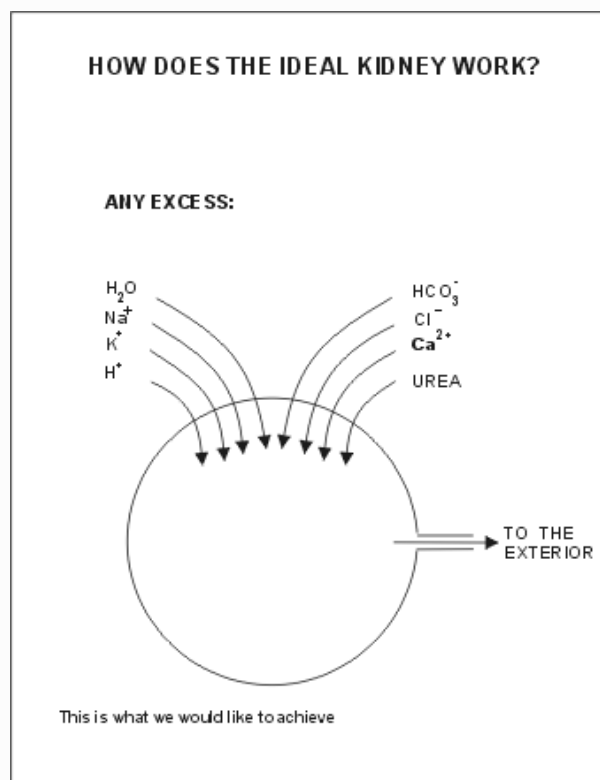South Africa

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WHAT NEEDS TO BE ACHIEVED?

We generally consume about 20-25% more salt and water per day than we would need (to make up for losses through sweat, exhaled moisture, and via the faeces) on an average day. That means that should the day be hotter than expected, or the faeces wetter than usual, there is no immediate crisis - we have a reasonable reserve of these valuable substances before we become thirsty, or start to crave salt.

On a normal, average day, therefore, that 20-25% excess water and salt has to be got rid of via the urine. The exact amount that has to be excreted depends on how "average" the day has been, and how much excess water and salt have, therefore, to be got rid of. Water volume sensors, salt sensors, osmolality sensors etc. determine how much the excess is, and they then instruct the kidney via a variety of hormones exactly what needs to be excreted, and in what quantities.

The ideal kidney would therefore consist of a simple bladder, lined by epithelium capable of pumping water, various salts and urea (plus a few other water soluble organic substances) from the plasma into the bladder, from where this material can be evacuated to the exterior.

The ideal kidney would therefore be a very simple organ:

HOW DOES THE IDEAL KIDNEY WORK?

ANY EXCESS:

H_2O
Na^+
K^+
H^+

HCO_3^-
Cl^-
Ca^{2+}
UREA

TO THE EXTERIOR

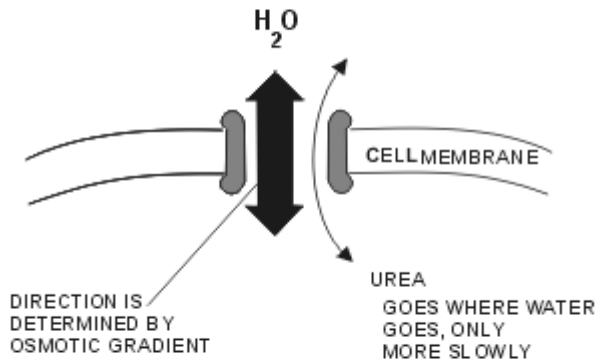This is what we would like to achieve

THE PROBLEM

The problem is that we have all the required pumps *except* water pumps and urea pumps. Considering how reliant we are on water and the movement of water across membranes to maintain the correct volumes of fluid in various body compartments, it is peculiar in the extreme that nature has never invented water pumps that use ATP to move fluid from compartment to compartment.

We also lack urea pumps. Urea diffuses through the water channels in cell walls, and simply goes wherever water goes.
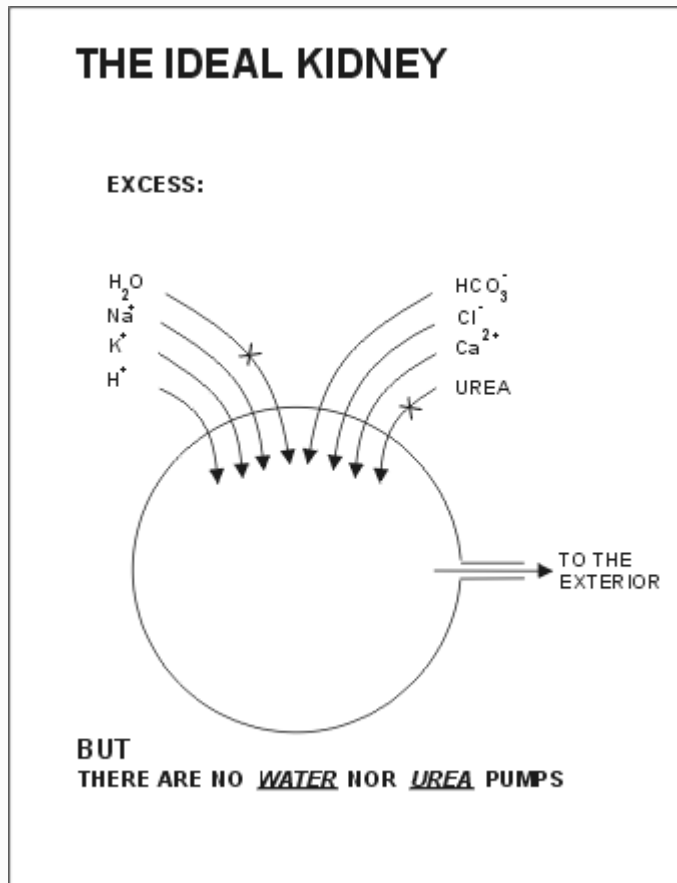
Cell membranes are equipped with water channels, called aquaporins (AQPs). AQPs are not "pumps". They are passive channels, through which water diffuses in a direction dictated primarily by osmotic forces. To cause a net movement of water from one compartment into another, salts (e.g. sodium chloride) have to be pumped across the membrane first, and water will then follow by osmosis. (Urea passively follows the movement of water, and is therefore more or less evenly spread through all the body's water compartments.)

AQUAPORIN WATER CHANNELS (AQP)

H$_2$O

CELL MEMBRANE

DIRECTION IS DETERMINED BY OSMOTIC GRADIENT

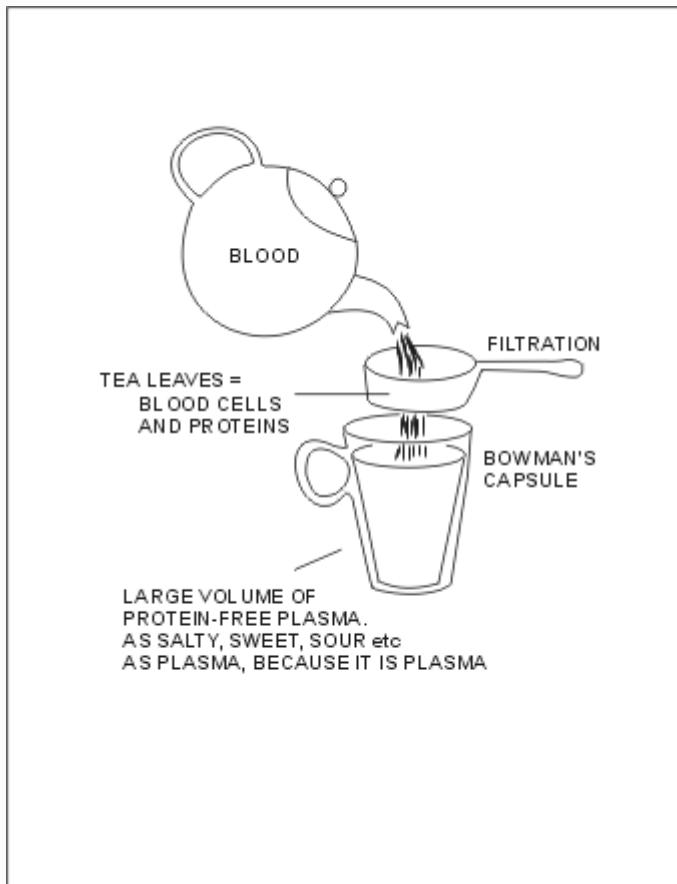UREA GOES WHERE WATER GOES, ONLY MORE SLOWLY

THE SOLUTION

To solve the problem of getting rid of the excess water and salts we consume per day, as well as disposing of the urea that is made, a completely different tactic has to be followed from the one suggested above as "the ideal kidney".

A very large volume of extracellular fluid is separated from the plasma per day, of which the bulk (99%) is reabsorbed back into the plasma, *leaving behind* the water, salts and urea we do not want to keep. It achieves exactly the same thing as the "ideal kidney", but in a rather laborious "back-to-front" manner.

This unusual, or counterintuitive, way of doing things is forced on us because we do not have water or urea pumps.

So,

we start by making a large volume of protein-free plasma (i.e. ordinary extracellular fluid, very similar, if not identical, in compostion to tears), at a rate of about 6 litres per hour:
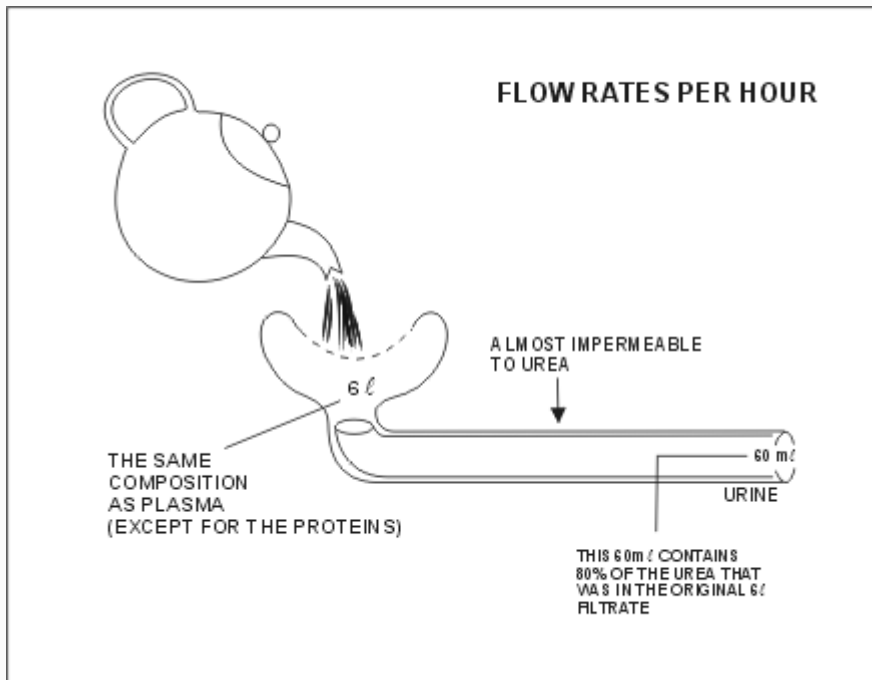
BLOOD

FILTRATION

TEA LEAVES =
BLOOD CELLS
AND PROTEINS

BOWMAN'S
CAPSULE

LARGE VOLUME OF
PROTEIN-FREE PLASMA.
AS SALTY, SWEET, SOUR etc
AS PLASMA, BECAUSE IT IS PLASMA

EXCRETION OF UREA WITHOUT THE BENEFIT OF UREA PUMPS.

The 6 litres of extracellular fluid (or "tears"!)created in this manner, will, over the course of 24 hours contain as much urea as we need to get rid of per day. Thus all that is required is that 99% of that fluid be reabsorbed as quickly as possible, before the urea has a chance to follow the water through the aquaporins . We will then be left with small volume of water (on average about 60 ml/hr) which contains all the trapped urea. This small volume of remaining water, with the urea that can now be discharged to the exterior, is called urine.

The 6 litres of fluid is therefore made to flow along a tube equipped with aquaporins that are relatively impermeable to urea. Salt and water are absorbed at as fast as possible from the tube, leaving most of the urea behind in the tube.

At the end of the tube the small amount of remaining water containing very nearly all of the original urea, is discharged into a bladder devoid of aquaporins. There the urine can await a convenient time for evacuation to the exterior.

FLOW RATES PER HOUR

ALMOST IMPERMEABLE TO UREA

6 ℓ

THE SAME COMPOSITION AS PLASMA (EXCEPT FOR THE PROTEINS)

60 mℓ

URINE

THIS 60 mℓ CONTAINS 80% OF THE UREA THAT WAS IN THE ORIGINAL 6ℓ FILTRATE
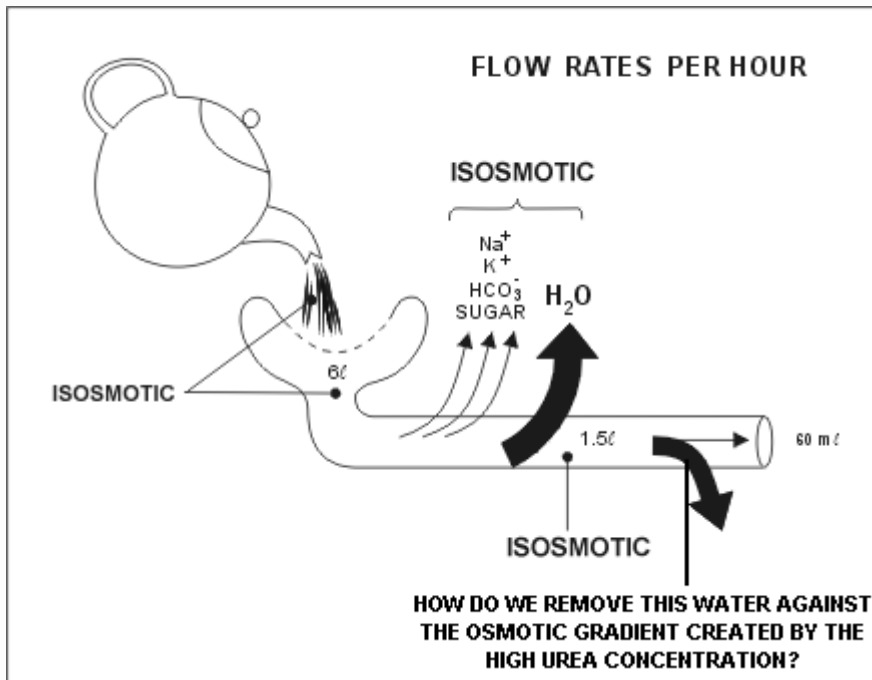
Thus, to excrete the urea, we remove the water (and all the other ingredients we would like to keep) as fast as possible from the 6 litres of filtrate, before urea has time to realise it is being left behind.

REMOVAL OF THE WATER

a. THE EASY PART

Salts (mainly sodium, potassium, chloride, and bicarbonate ions), plus glucose and amino acids are actively pumped out of the tubule back into the plasma, using ATP as fuel. Water follows as a result of the osmotic gradient that this movement of solutes creates.

The fluid removed from the tube is therefore isosmotic, and so is the fluid that remains in the tube. The remaining tubular fluid (reduced from 6 litres to 1.5 litres per hour) now no longer contains any glucose or amino acids, and has a far lower concentration of salts than plasma. But what it is missing in glucose and salts etc, is made up for, osmotically, by the urea that is left behind. Its concentration is four times higher than it was in the original 6 litres of glomerular filtrate (and in the rest of the body fluids).

FLOW RATES PER HOUR

ISOSMOTIC

Na$^+$
K$^+$
HCO$_3^-$
SUGAR   H$_2$O

ISOSMOTIC

6ℓ

1.5ℓ   60 mℓ

ISOSMOTIC

HOW DO WE REMOVE THIS WATER AGAINST
THE OSMOTIC GRADIENT CREATED BY THE
HIGH UREA CONCENTRATION?

REMOVAL OF THE WATER
b. THE DIFFICULT PART

To remove the remaining 1.5 litres (per hour) of precious water from the tubular fluid, we need a hyperosmotic environment round the distal portion of the tube (i.e. the peritubular environment must have a higher osmolality than that of the ~ 60 ml urine we eventually intend to excrete).

This is not a problem with a straight forward answer. It means isolating a region in the kidneys where the extracellular environment is very different from that in the rest of the body. Such special environments can only exsist, and be maintained if use is made of counter-current mechanisms.

The area of the kidney that can be isolated from the rest of the kidney tissues, and be made hyperosmotic (3-4 times the osmolality of the rest of the body) is the "renal medulla".

To achieve this, therefore, first bend the tube into a U-tube, which dips into the renal medulla.

FLOW RATES PER HOUR

4.5 ℓ

6 ℓ

1.5 ℓ
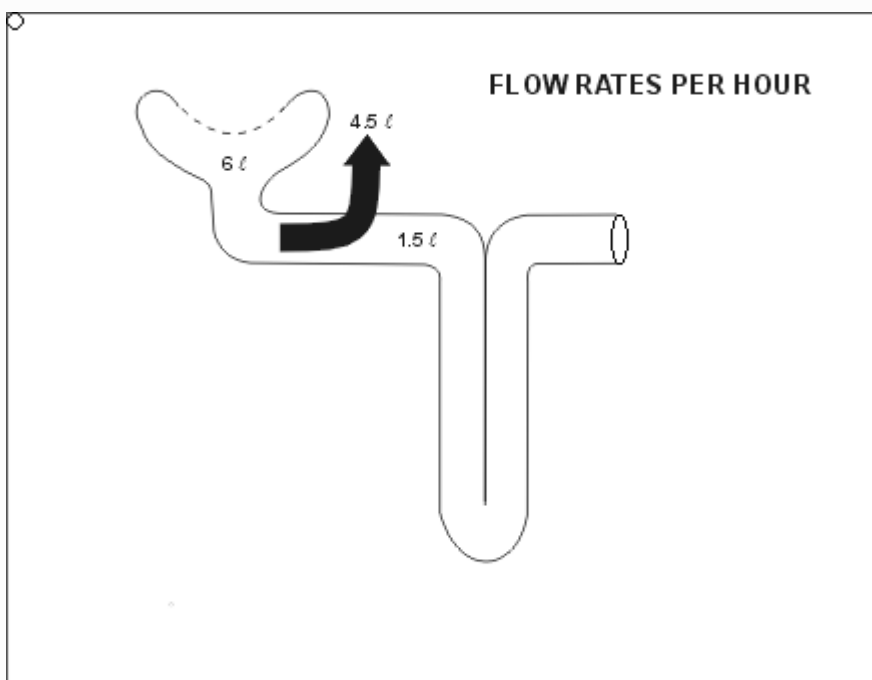
Ensure that there are no aquaporins in the ascending limb of the U-loop.

FLOW RATES PER HOUR

6 ℓ

1.5 ℓ

NO AQP's
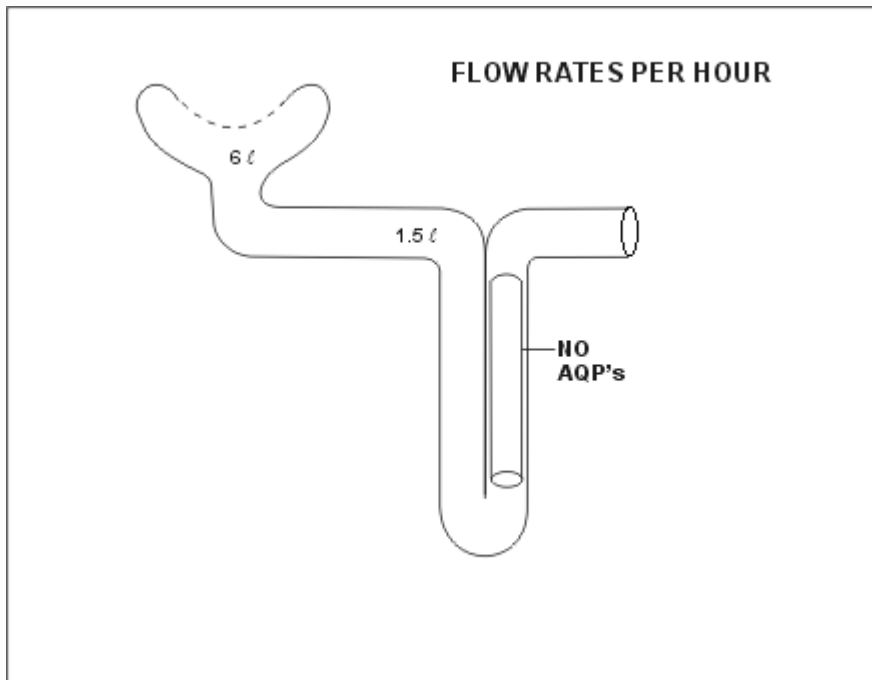
Then actively pump salts (chloride and sodium ions) from the ascending limb into the descending limb of the U-tube. (The U-tube is called the "Loop of Henle", after its discoverer.) Since there are no aquaporins in the ascending limb, water cannot follow this movement of salts.

FLOW RATES PER HOUR

6 litres

1.5 litres   1.5 litres

INCREASING OSMOLALITY
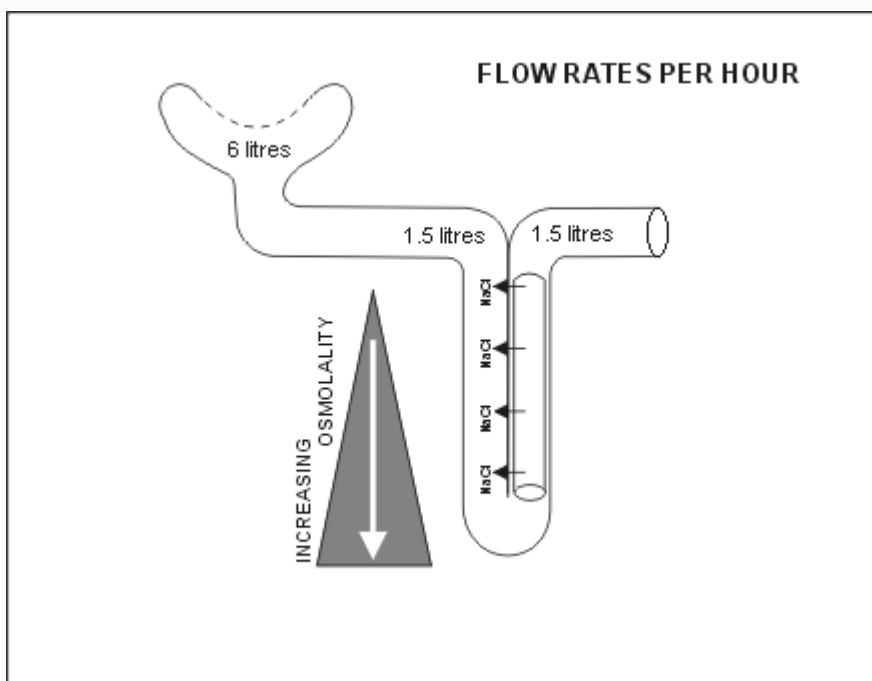
NaCl
NaCl
NaCl
NaCl

The osmolality of the fluid going down the descending limb of the loop will therefore increase as it gains more and more NaCl unaccompanied by water. On the way up the ascending limb of the loop the osmolality decreases again (because the salts in this fluid are being transferred, without water, to the descending limb).

At the top of the ascending limb of the loop one would expect the osmolality to have returned to what it was before the fluid entered the loop. Its volume would also be expected to be 1.5 litres per hour. Superficially it would seem, therefore, that nothing at all has been achieved by the insertion of this U-tube into the system.However, at the hairpin bend of the loop, the fluid in the tube has become extremely hyperosmolar. In

the human kidney the osmolality is 3-4 times that found anywhere else in the body!

This hyperosmotic fluid in the tip of the loop will therefore absorb water from its surroundings (by osmosis), creating a very dry, hyperosmotic environment in its immediate vicinity (i.e. in the renal medulla). This is exactly what we require to remove most of the 1.5 litres/hr of tubular water which remains after the isosmotic absorption which occurred in the first part of the tubule. All that is required is that we send the last portion of the tubule through the hyperosmotic environment we have just created:
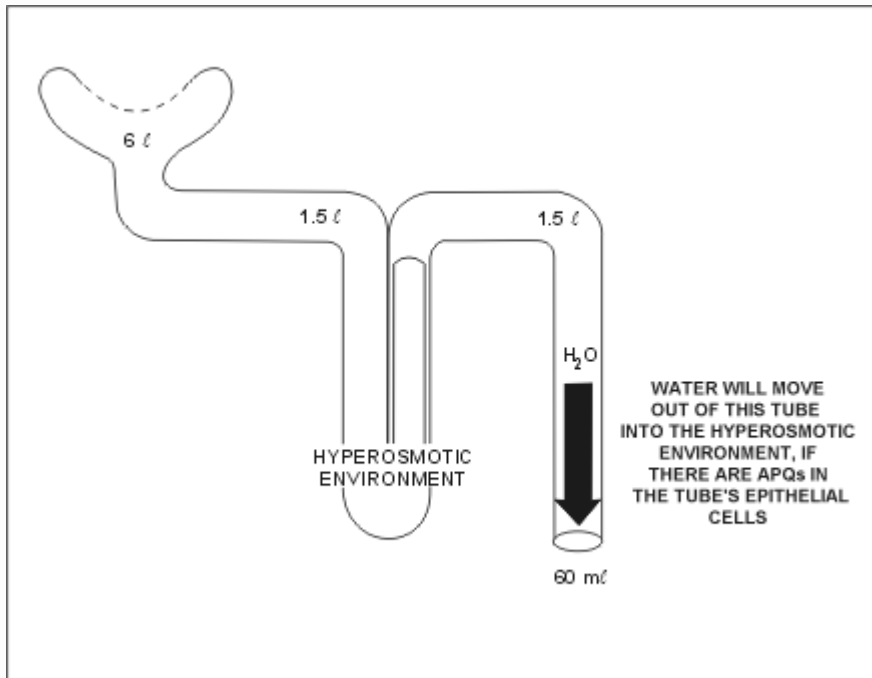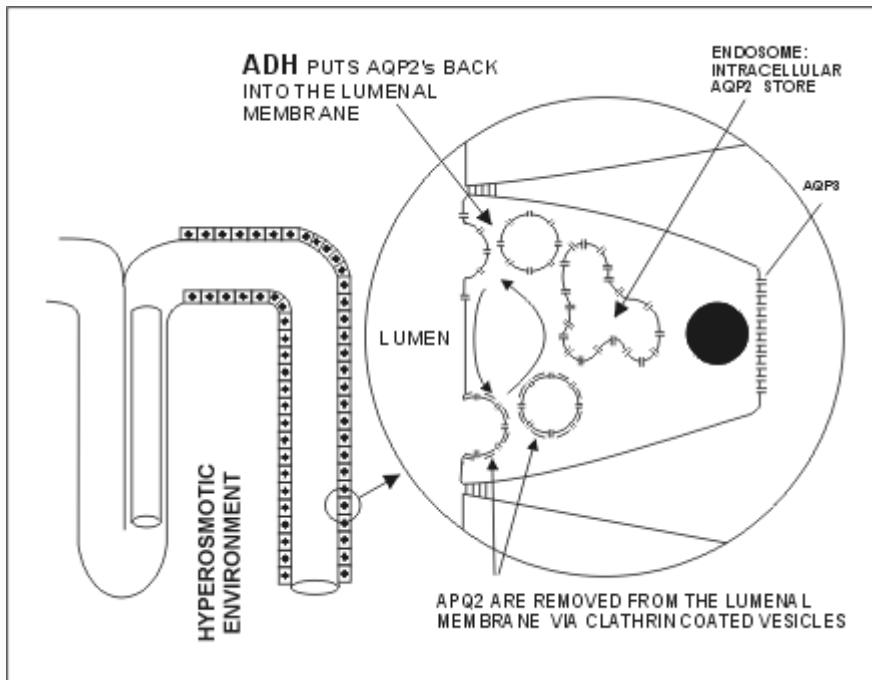

The final portion of the tubule which goes through the hyperosmotic environment created by the counter-current mechanism we have inserted into the system, is called the "collecting duct". This is because it collects fluid from several tubules, each of which, at its termination, would only be delivering a very small dribble of urine, when the final reabsorption of water is complete. Note: the "60 ml" refers to the total urine volume formed by all the tubules, which number many millions. So each one produces only a miniscule drop of urine per hour.

The epithelium of the collecting ducts has the ability to insert aquaporins, called APQ2s, into its lumenal membrane or not, depending on the instructions received via the hormone ADH (anti-diuretic hormone). If ADH is present in the blood, aquaporins are taken from the epithelial cell's internal stores and placed in the lumenal membrane.

If this happens, then the hyperosmotic environment surrounding the collecting duct will draw water from the collecting duct by osmosis. This can, under extreme circumstances, reduce the final flow in the tubule to about 15 ml (about a tablespoonful) per hour.

ADH PUTS AQP2's BACK INTO THE LUMENAL MEMBRANE

ENDOSOME: INTRACELLULAR AQP2 STORE

AQP3

LUMEN

HYPEROSMOTIC ENVIRONMENT

APQ2 ARE REMOVED FROM THE LUMENAL MEMBRANE VIA CLATHRIN COATED VESICLES

In the absence of ADH, the collecting ducts are impermeable to water. The hypersomotic environment surrounding the collecting ducts therefore has no effect on the fluid in the tubule, and the urinary flow rate can be as high as 1500 ml per hour. (See also the comments on the hormone ANP, below.)

NOTE:

> The flow rate of about 60 ml per hour referred to in the previous diagrams is an approximate average; but it should be remembered that there is nothing "normal" about this flow rate. The "normality" of urinary flow rate resides in the fact that it is never ever the same! An unchanging urinary flow rate is an absolute sign of kidney function failure. The urinary flow must vary, and must always be changing over a very large range (15 ml to 1500 ml/hr) to be normal.

> The urine's composition must similarly vary incessantly over a very wide range to be normal. It is therefore fallacious in the extreme to speak of "normal" urine:

THE ONLY NORMAL URINE, IS ABNORMAL URINE!

The fluid that escapes from the collecting ducts will obviously dilute the hyperosmotic tissue environment created by the loops of Henle. However, the fluid in the hairpin bends of the loops remains hyperosmotic (because of the constant pumping of salt from the ascending limbs to the descending limbs of the loops), and will quickly absorb this water from the tissues.

Once the water has entered the hairpin bend, it immediately flows into the ascending limb of the loop from which it cannot escape, as there are no aquaporins in this portion of the tubule. The flow rate through the ascending limb of the loop is therefore greater than the flow rate through the descending loop.

The overall effect is that, in the presence of ADH in the blood, water leaves the collecting ducts (via osmotic forces), passes into the surrounding tissues, from where it is absorbed into the hairpin bends of the loops of Henle (also via osmotic forces), and is then carried up the ascending limbs of these loops to the ends of the loops. These are situated in the "cortex" (as opposed to the "medulla") of the kidney. More fluid therefore exits from the loops than went into them at the beginning. Furthermore, since they contain more water than they did at the start of the loop, the fluid is also hypo-osmolar (i.e. more dilute) with respect to that initial fluid, and, therefore, also with respect to plasma.

The portion of the tubule between the end of the loop and the beginning of the collecting duct is called the "distal convoluted tubule", or "distal tubule" for short.

In the presence of ADH in the blood, there will be aquaporins in the epithelium of the distal tubules (as well as in the epithelium of the collecting ducts). Since the fluid entering the distal tubules is hypo-osmolar with respect to plasma, water will be drawn out of the tube into the plasma, until the osmolalities equalize. The remaining water enters the collecting duct from where it can be removed from the urine by the mechanism described above.

Thus, in the presence of ADH, water that enters the collecting ducts is removed by osmotic forces into the hyperosmolar tissues of the renal medulla. From there it is absorbed into the hairpin bends of the loops of Henle, carried up the water-tight ascending limbs of the loops to the distal convoluted tubules in the cortex of the kidney, from where this water is finally drawn back into the plasma, once again by osmotic forces.

ADJUSTING THE AMOUNT OF SALTS IN THE TUBULAR FLUID DESTINED TO BE EXCRETED:

The final adjustments to the sodium, potassium, ammonium, chloride, bicarbonate, and hydrogen ion amounts that are to be excreted in the urine, are made in the distal convoluted tubule. If the amount of ion "X" in the fluid at this point is less than the amount you wish to get rid of (to keep its concentration in the body fluids at the correct level), then "X" will be pumped from the plasma into the tubule. If you have already excreted all the "X" you wish to excrete for the day, then any "X" in the distal tubular fluid will be removed, and no further "X" will appear in the urine.

The decision to add or remove "X" from the distal tubular fluid is based on information gathered by sensors which measure the concentration of "X" in the arterial plasma. This information is then relayed to the kidneys by hormones. The kidneys blindly carry out the instructions received via the hormones, doing whatever the hormones tell them to do. The kidneys make no independent decisions on these matters! If they do, as sometimes happens, then there is serious pathology.

THUS, WE HAVE ACHIEVED WHAT INITIALLY APPEARED TO BE IMPOSSIBLE:

We have removed everything (salts, sugar, water etc.) that we did not want to lose from the original 6 litres/hr of extracellular fluid that entered the tubule, leaving behind a small volume of water (varying between 15 ml/hr and 1500 ml/hr, but usually around 60 ml/hr) with a high concentration of urea, and only the unwanted excess salts we had taken in with our diet.

And we did all of this without the benefit of water or urea pumps!

A second hormone ANP (atrial natriuretic peptide) can also influence the rate of water excretion via the urine, using a different mechanism of action. When it is present in the blood it causes an increase in the rate of glomerular filtration:
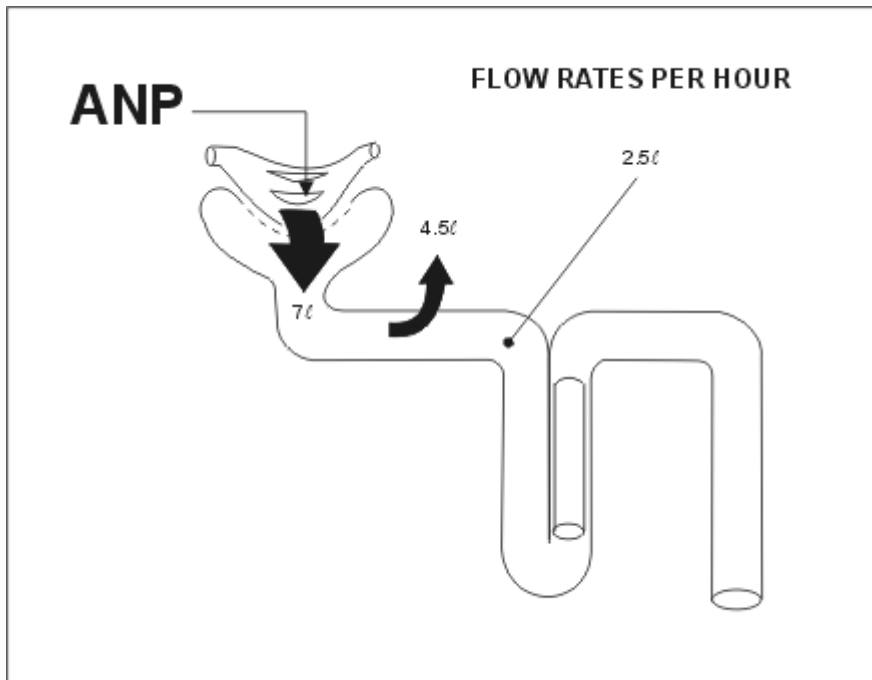
We assume, for the sake of simplicity, that ANP has caused an increase in the rate of glomerular filtration from 6 litres/hr to 7 litres/hr.

Since the rate of reabsorption of isosmotic fluid from the proximal tubules remains unchanged, ANP causes, in this example, an approximate 60% increase in the flow rate through the Loop of Henle, greatly diminishing its effectiveness as a generator of an hyperosmotic environment in the renal medulla:

Consider the following:

> If 500 mmol Na^+ and 500 mmol Cl^- are pumped per hour from the ascending limb of the Loop of Henle into the descending Loop of Henle, and the flow rate through the loop is 1 litre per hour (to make things easy), then 1000 mosmol of osmotically active particles are added to each litre of tubular fluid as it descends towards the hairpin bend of the Loop of Henle. The osmolarity therefore rises by 1000 mosmol/l from the beginning of the descending limb to the hairpin bend (and decreases by this amount as it rises up the ascending limb of the Loop of Henle).
>
> Should the flow rate through the Loop increase from 1 litre per hour to 2 litres per hour, and the transfer of NaCl from the ascending limb into the descending remain unchanged (the NaCl pumps in this part of the nephron work at a fixed rate as far as we are aware), then 1000 mosmols are added to TWO litres of water per hour (instead of 1 litre per hour). The osmolarity of the tubular fluid at the hairpin bend will therefore be only 500 mosmol/l higher than at the beginning of the Loop.
>
> An increase in the flow rate through the loop from 1 litre to 3 litres per hour will reduce the increase in osmolarity by only 333 mosmol/l (instead of by 1000 mosmol/l).
>
> The decrease in osmolarity at the hairpin bend resulting from an increase in the flow rate through the Loop of Henle severely diminishes the hyperosmotic environment that is available for the removal of water from the collecting duct under the influence of ADH.

In addition to the above effect, a much larger volume of tubular fluid enters the distal convoluted tubule and the collecting duct than usual, from which a much smaller proportion of water than normal can be reabsorbed (due to the reduction in hyperosmolality in the medulla).

ANP therefore causes loss of water and salt via the urine.

THUS:
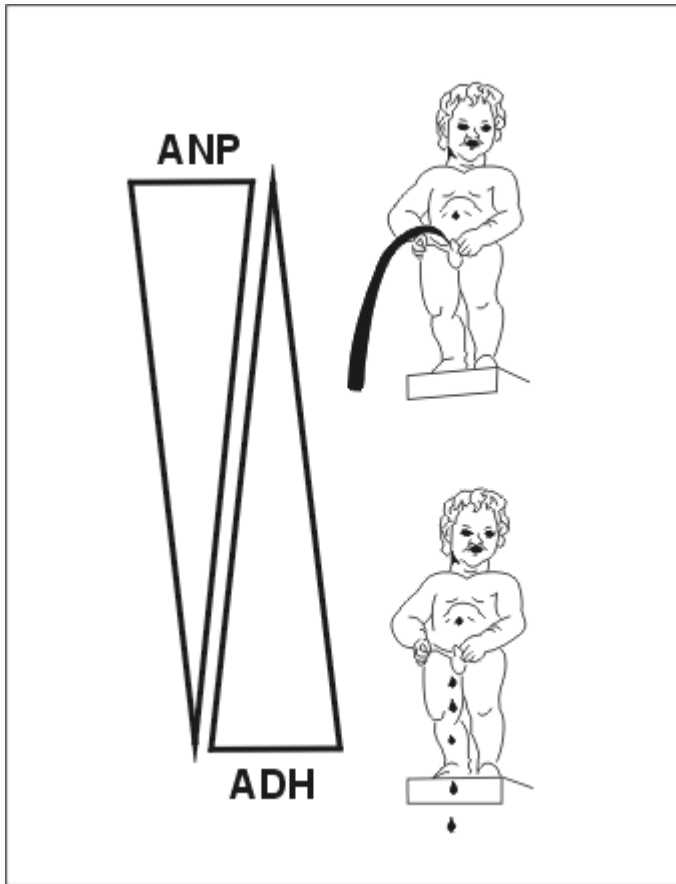
Note:

Almost the only substances ("waste products") which are SECRETED INTO the proximal tubular fluid (whereas everything else is REMOVED from the tubular fluid, leaving behind only what is considered excessive to be excreted in the urine) are "drugs". These are all the "poisonous" substances contained in vegetables, herbs, spices, nuts, grain, and fermented products such as bread, cheese, wine, tea, coffee and chocolate etc. which plants and fungi produce to limit their consumption by animals. ("Drugs", of course, also include the concentrates of these plant, fungal and bacterial substances which can be bought at the pharmacist.)

Except for this, and the disposal of urea, the kidneys are not, strictly speaking, organs that get rid of "waste products" from the body. They are primarily organs that dispose of excess salt and water consumed during a normal day.

Illustrations by Ann Koeslag (Mail me)