# The Vulcan kidney

**Douglas R. Waud**

One can often gain new insights into a topic when approaching it from a new angle. The paradigm example involves the insights into histology that can be gained from studying pathology. For example, a rare cell type in the pituitary suddenly becomes very easy to recognize once a whole field of them can be seen in a tumour. Similarly, one can gain insights by looking at species other than our own. In this article, **Doug Waud**, using the kidney in Vulcans, takes this latter theme one step further to provide useful insights into renal physiology and pharmacology.

I enjoy teaching. I like the challenge associated with identifying ways to clarify concepts. One area I have found to be particularly difficult for medical students to understand is the reasoning underlying the notions of osmolar clearance and free water clearance. I struggled for years trying to get the basic idea across to medical students without the impression that I was having much success. A few years ago I stumbled onto an approach that seems to work. Because I believed this story might be of interest to more than just my own classes, I decided to put it down in writing.

I shall assume that the reader has been exposed to renal physiology but long enough ago that the details might now be a bit hazy. So, we can begin with a brief review. I shall focus on only those features of nephron behaviour that we shall need for the present purpose.

The behaviour of the kidney is essentially the sum of the behaviours of its component units, the nephrons. These in turn consist of the sequence glomeruli, proximal convoluted tubule, descending limb, ascending limb, distal convoluted tubule and collecting duct. Much of the physiology of these units is derived from three basic approaches.

First, one can do micropuncture studies which allow one to measure volume flow at various positions along the nephron. For example, one finds that flow out of the proximal convoluted tubule is greater than that out of the descending limb. Thus, one concludes that water is reabsorbed in the descending limb. Conversely, the flow into the ascending limb matches that out of the distal convoluted tubule. Therefore, we can conclude that water is reabsorbed in neither the ascending limb nor the distal convoluted tubule.

Second, one can do micropuncture studies to analyse solute content. For example, the amount of solute coming out of the descending limb matches that coming in, so it can be concluded that no salt is reabsorbed in that segment. Conversely, one finds that a lot of salt is reabsorbed in both the ascending limb and distal convoluted tubule.

Third, one can stick a microelectrode into the lumen and measure electrical potential. In the ascending limb this is positive. This can be interpreted as an indication that the prime mechanism reabsorbing the salt is some sort of pump which 'grabs at' $Cl^-$ ions. To see the argument here, work backwards. Imagine a pump that sucks $Cl^-$ ions out of the lumen. That should make the lumen relatively positive (relatively because that positive tendency will create a voltage gradient such that $Na^+$ ions will follow the $Cl^-$). The experts will come up with a fancier model (usually involving the buzz-word 'coupled') but we need not get into these details here. In the distal convoluted tubule the lumen is negative. This tells us that the 'pump' is probably a sodium pump here. The main point is that the pumps in these two segments are different and this implies we should end up with drugs that act selectively. And that, as we shall note later, is indeed the case.

## Renal 'work'

Although details such as we have been discussing are useful starting points, we really want a higher-level view. One I find particularly useful involves simply thinking about what the kidney has to do. The starting point is our aquatic ancestors who lived in the ocean. Their kidneys had a much simpler task. The environment was at the 300 mOsm level they needed to maintain in their *milieu internale*. Contrast this with land animals. In the desert, they must be able to concentrate urine to avoid unnecessary loss of water as they excrete salt. Conversely, they must be able to put out dilute urine if they are drinking a lot.

Thus, we can picture our kidney in three possible states: concentrating, diluting or (rarely) doing neither. The renal physiologists summarize this with the equation: $\dot{U} = C_{osm} + C_{H_2O}$, which says that urine flow ($\dot{U}$) consists of two components, osmolar clearance ($C_{osm}$) and free water clearance ($C_{H_2O}$). Thus, if the second term is zero, we have the case of the kidney doing no work. If the second term is positive it is doing work of dilution; negative, work of concentration. I suspect the reader can see that the equation does, indeed, parallel what I was saying about concentrating and diluting, but will not have any sense of understanding what, indeed, those two clearances really mean.

That is the educational dilemma I faced. We can now turn to the solution.

## The Vulcan kidney

In the past, I have found that it is possible to free oneself of entrenched biases by moving to some *terra incognito*. For example, I have used Martian physiology to clarify some pharmacokinetic ideas. With the renal problem, it seemed to me that the Vulcan physiology was the key. You might recall that Vulcans, exemplified by Spock,

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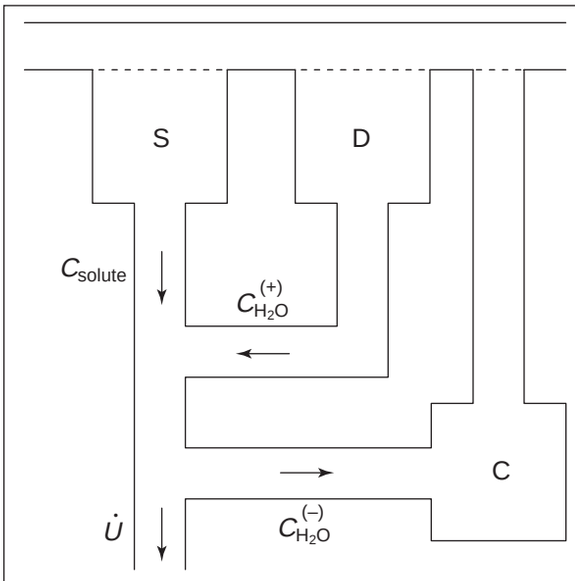


**Fig. 1.** Diagrammatic representation of the flow from the solute (S), diluting (D) and concentrating (C) Vulcan kidneys and their relationship to urinary flow. The arrows indicate the osmolar clearance, the two possible free water clearances and the total urine flow. $C_{H_2O}$, free water clearance; $C_{solute}$, solute clearance; $\dot{U}$, urinary flow.

show one key feature (apart from having pointed ears) – they are very logical. And this logic extends to their kidneys.

In fact, the Vulcans have three kidneys. First they have what is called the solute kidney. This kidney puts out the requisite amount of salt but it can neither concentrate nor dilute. The flow out of this kidney is called the solute clearance ($C_{solute}$). The next kidney is called the diluting kidney. This kidney does not deal with salt at all (no problem because the salt kidney takes care of that). The diluting kidney merely puts out water. Finally, we have the concentrating kidney. It too does not deal with salt. All it does is suck water back into the body from the urine.

Now, this layout emphasizes a key point. It is not logical to have the diluting kidney and the concentrating kidney working at the same time. This is the key point, which is obvious when you look at the Vulcan system but not so obvious in our kidney. However, later we shall go back and map the Vulcan system onto ours and, when doing so, remember that our kidney too might be concentrating or diluting, but not both at once.

Now, the flow out of the Vulcan solute kidney is called the solute clearance ($C_{solute}$), and that out of the other two is called the free water clearance ($C_{H_2O}$). This is positive if the diluting kidney is working and negative if the concentrating kidney is working. The sum of the two is the urinary flow. Thus, we have: $\dot{U} = C_{solute} + C_{H_2O}$. Alternatively, this can be summarized pictorially (Fig. 1).

Finally, note how those logical Vulcans called that first clearance solute clearance and not osmolar clearance. Indeed, it is this latter unfortunate choice of label on our planet that, in my opinion, underlies much of the confusion as to what osmolar clearance really means. I strongly recommend that you mentally replace osmolar clearance with solute clearance any time you encounter the term.

That diagram of the Vulcan kidney helps us to see why a 'clearance' of salt would take the dimensions of a volume of water per unit time. This is simply to avoid adding peaches and pears. We want to divide the urine flow into its two functional components: the output associated with no work of concentration or dilution, and the remainder. It is obvious that the urine flow and the free water clearance are going to be in ml $min^{-1}$ so we have

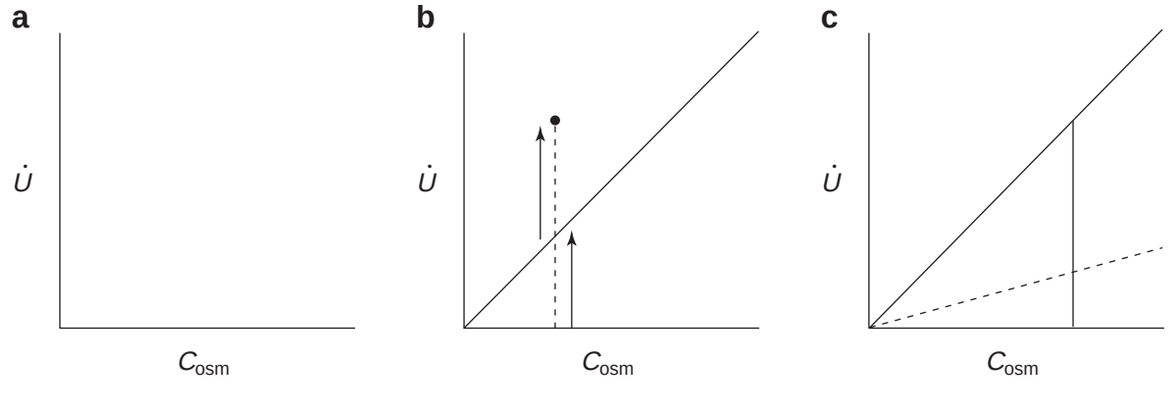


**Fig. 2. a:** Plot of urine flow ($\dot{U}$) against osmolar clearance ($C_{osm}$). **b:** Free water clearance. The diagonal represents free water clearance equal to zero, when the kidney is neither concentrating nor diluting (urine osmolarity is 300 mOsm). The diagonal is set at an angle of 45°, which means that, for the point represented by the black circle, the vertical distance (labelled with the vertical arrow to the right of the vertical broken line) from the scale of abscissa to the diagonal will be equal to the abscissa of that point, that is, numerically equal to the osmolar clearance. Urine flow is represented by the length of the vertical line from the scale of the abscissa to the black circle, the part below the diagonal is osmolar clearance and that above is free water clearance. Therefore, free water clearance is represented by the arrow to the left of the vertical broken line. If the point is below the diagonal, the urine flow will be less than the osmolar clearance and the free water clearance will be negative. **c:** The vertical line is drawn at a given level of osmolar clearance. The top of this line (on the diagonal) represents the urine flow for that level of solute output that is consistent with a urine osmolarity of 300 mOsm. The broken line represents an osmolarity of 1200 mOsm.

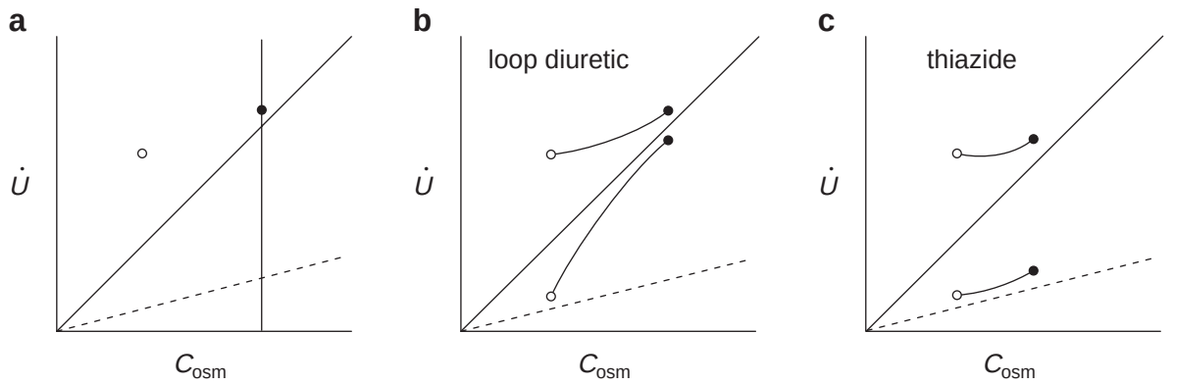


**Fig. 3.** The effects of loop diuretics and thiazides on the diluting or concentrating kidney. **a:** Basic approach, illustrated with a loop diuretic in a diluting kidney. The increased salt loss implies $C_{osm}$ will increase so we move from the starting point (open circle) to some place on the vertical line. Such a drug also decreases production of free water so we must move closer to the diagonal line. Both these shifts bring us to the filled circle. **b:** Summary for a loop agent. Diluting case as in a. Concentrating case starts at the open circle below the diagonal and increase in salt loss moves us to the right, to some place on that vertical line. Because the loop agents interfere with maintaining papillary osmolarity, the ability to concentrate is hampered so we must also move closer to the diagonal – to the filled circle. **c:** Summary for a thiazide. For the diluting kidney the argument parallels that for the loop agents except for a milder rightward shift. For concentrating kidney, there is no interference with papillary osmolarity so we move horizontally to the right (or nearly horizontally in the real world). $\dot{U}$, urine flow; $C_{osm}$, osmolar clearance. Diagonal, urine osmolarity 300 mOsm; dotted line, urine osmolarity 1200 mOsm.

to get the solute clearance into the same dimensions. If we are dealing with a 300 mOsm solution this does the job. We can do this either conceptually with our kidney or directly by inspection with the Vulcan kidney. The latter route tends to be easier.

## A second look at our nephron

So, returning to earth, we can ask: where is our diluting kidney anatomically? Alternatively, we can ask where we make positive free water. The key is to look for a segment where we reabsorb solute unaccompanied by water. As I indicated earlier, this happens in the ascending limb and distal convoluted tubule. So, we conclude that the ascending limb and distal convoluted tubule constitute our equivalent to the Vulcan diluting kidney.

And where is our concentrating kidney? Or, where do we make negative free water? This time we look for a place where we reabsorb water unaccompanied by salt. This occurs in the descending limb but more significantly in the collecting duct. I say 'more significantly' and focus here on the collecting duct because that is where the final adjustments occur that determine the ultimate result. Indeed, the collecting duct, you may recall, has a lining that can be altered selectively in the presence of antidiuretic hormone such that water permeability increases. This puts the lumen of the collecting duct in aqueous continuity with the interstitium of the renal papilla, an environment which has a high solute concentration – one so high that the osmolarity is 1200 mOsm. Thus, if the urine is more dilute than 1200 mOsm, water will flow down a concentration gradient out of the lumen into the interstitium. The urine will be concentrated. So we map the Vulcan concentrating kidney to our collecting duct.

An aside on the hyperosmotic papillary interstitium is in order. Note that it is that salt reabsorption in the ascending limb which generates that 1200 mOsm concentration. As the salt is 'pulled out' of the lumen it ends up in the interstitium. Thus, this leads to the interesting observation that this salt reabsorption in the ascending limb underlies not only the diluting of urine but also its concentration. I believe this is one reason why students find the area confusing. However, the Vulcan analogue comes to the rescue. It shows us that, although the processes are linked, we must still consider them to be distinct and, in particular, not to picture them both being used at the same time.

## The pharmacology

Most of pharmacology is very simple. You start with the underlying physiology or biochemistry and just tie in the drugs. The area we have been discussing is an example on the physiological side. Specifically, we can consider two classes of drug as examples, the 'loop' or 'high ceiling' diuretics and the thiazides. We can summarize the pharmacology of the high ceiling class, furosemide, ethacrynic acid and friends, by noting that they block salt reabsorption in the ascending limb. The thiazides, like hydrochlorthiazide, block the reabsorption of salt in the distal convoluted tubule. (Earlier I noted that we might expect to be able to affect these two 'pumps' selectively; here we now have specific examples.)

## The deductive aspect

Implicit in what I said about the pharmacology is that, once you have the drug in context, you should be able to deduce a lot about how it behaves. I now wish to

illustrate this with a reasonably demanding quantitative example.

### A frame of reference

I shall use a plot of urine flow against osmolar clearance as a frame of reference (Fig. 2a). Now, the teacher in me is going to drag you back to first principles. When we encounter a plot we first must put it in context.

We can start by asking what determines where a point lies on that plot, i.e. what determines the ordinate and the abscissa. The ordinate is urine flow and a simple recollection of one's experience tells you that urine flow will reflect water input. There can be some fine-tuning adjustments for insensible respiratory losses and sweating, for example, but the 'bottom line' remains – if you don't put out as much as you take in you turn into a wet sponge; if you put out too much you turn into a prune. Similarly, the abscissa will reflect how much salt we took in. So now we can see why this diagram might have been chosen originally. It is set up to summarize the two main jobs of the kidney – looking after water and salt balance.

Now, our earlier frame of reference – looking at the activities involving no work and work, or both, on the part of the kidney – needs to be tied in. The easiest way to do this is to consider first the simplest case we can find. This will be a kidney that is doing neither the work of dilution nor of concentration. In this case, the free water clearance will be zero and we can write simply: $U = C_{osm} + C_{H_2O} = C_{osm}$ which, on our graph will be a straight line at an angle of 45°. We can label this line either 'free water clearance = zero', '300 mOsm' (the osmolarity the urine will show if the kidney is neither concentrating nor diluting), or 'no work'.

Our diagram includes urine flow and osmolar clearance (on the axes) but we need to be able to see free water clearance because it tells us about the work of concentration or dilution. If you think about this for a moment you should be able to come up with something along the lines of Fig. 2b. Here, free water clearance is the distance the operating point in question lies from the diagonal – in the diagram, represented by that arrow to the left of the vertical broken line. If the point is below the diagonal the urine flow will be less than the osmolar clearance and the free water clearance will be negative as it should be.

We shall need one more insight. Earlier we noted that the kidney concentrates urine by sucking water into an area at 1200 mOsm. This tells us that the upper limit to urinary concentration will be 1200 mOsm. Where does this lie on our graph (see Fig. 2c)? I have drawn a vertical line at some value of osmolar clearance. The top of that line, on the diagonal, represents the urine flow for that level of solute output that is consistent with a urine osmolarity of 300 mOsm. What would the urine flow be if the urine was twice as concentrated? Well, with the same amount of salt and twice the osmolarity, we would have half the urine flow so we'd be only half way up the line. Similarly, if the urine is 1200 mOsm, four times as concentrated as 300 mOsm, we would be only one quarter of the way up that line. This geometry would apply wherever we draw that vertical line. Thus we can draw that broken line at one quarter the slope of the diagonal as our 1200 mOsm lower boundary. (One can similarly identify an upper boundary at about 60 mOsm but we need not get into that here.)

### The drug actions

Now we can deduce what our drugs will do (and, in the process, illustrate how we can both do a very respectable quantitative job, and illustrate subtle differences between two classes of drug).

Let us start with the high-ceiling diuretic. First we must think logically like Vulcans and recognize that we must consider two cases – a kidney which is diluting then one which is concentrating.

With the diluting kidney we can start at the open circle in Fig. 3a. We are asking where this point will move in the presence of the drug. We approach it in two steps. First we see how it shifts horizontally, then vertically. When we add a loop diuretic we block reabsorption of salt in the ascending limb. This means we shall see more salt coming out into the urine. This, in turn, means that the osmolar clearance will have to go up. In Fig. 3a I represent that by a shift to somewhere on that vertical line.

To see what happens in the vertical direction we focus on free-water clearance not urine flow because it is the free water clearance that has more functional meaning to us. If we have a drug which blocks that reabsorption of salt in the ascending limb we have a drug that reduces the production of free water. Thus, our point must approach the diagonal. When we put this all together we deduce a path over to the point indicated by the closed circle in Fig. 3a. Now we consider the case when the kidney is concentrating. Again we deduce that the osmolar clearance will rise so again we expect a shift to the right in our diagram. Now we look at the vertical direction. If we block the reabsorption of salt in the ascending limb we will block the generation of the 1200 mOsm osmolarity in the papilla and therefore interfere with our ability to concentrate urine or, what is equivalent, make negative free water. We have disabled the concentrating kidney. Thus our point will again move toward the diagonal, this time heading upwards. This can be summarized in Fig. 3b.

Now we can play the same game with the thiazides. Again we have a drug that interferes with reabsorption of salt. This occurs at a different segment of the nephron but the end result on osmolar clearance is the same – and increase reflecting an increased loss of salt. The shift to the right this time will tend to be less than that seen with the high-ceiling diuretics (they come by that name honestly) but otherwise the situation is similar. With the patient diluting urine the story is also similar to that with the loop agents. The thiazides interfere with reabsorption of salt unaccompanied by water so they reduce the

ability of the kidney to make free water so our point should not only move to the right it should get closer to the diagonal.

With the patient concentrating urine we get the *pièce de résistance*. In contrast to the loop diuretics, the thiazides interfere with reabsorption of salt at a locale removed from the papilla so they do not interfere with maintenance of that 1200 mOsm region surrounding the collecting duct. The kidney does not lose its ability to concentrate; it can still make negative free water. Our point will not move toward the diagonal as we saw happen with the loop agents. Where will it go? Well, the kidney still has the assignment of keeping the urine flow low to maintain water balance. Thus, we would expect the compensation would probably not be perfect so we might expect the point actually to move to the right and slightly upwards. The action of the thiazides can be summarized in Fig. 3c.

### Concluding remarks

Note how, starting from the physiology and just a minimal indication regarding the site of action of the drugs, we can make some quantitative deductions as to what the drugs will do. This is a nice illustration of what pharmacology is all about. There is more to it than just that horrible list of drug names all physicians recall from their medical student days. Unfortunately, one cannot really appreciate the conceptual aspect on the first round because it is clouded by all that memorization of names. This story might help to show you some of the pretty stuff that you might have missed first time around.

# Neurotrophins and depression

**C. Anthony Altar**

Exogenous delivery of the neurotrophic factors, brain-derived neurotrophic factor (BDNF) or neurotrophin-3 (NT-3), promotes the function, sprouting and regrowth of 5-HT-containing neurones in the brains of adult rats. Similar infusions of BDNF into the dorsal raphe nucleus produce an antidepressant effect, as evaluated by several 'learned helplessness' paradigms. Environmental stressors such as immobilization induce depression and decrease BDNF mRNA. Antidepressants increase BDNF mRNA in the brain, via $5\text{-HT}_{2A}$ and β-adrenoceptor subtypes and prevent the stress-induced decreases in BDNF mRNA. In this article, **Tony Altar** discusses how existing treatments of depression might work by increasing endogenous brain levels of BDNF or NT-3, which in turn could promote monoamine-containing neurone growth and function. Drugs that selectively stimulate the production of neurotrophins could represent a new generation of antidepressants.

Depression is a potentially life-threatening disorder that affects hundreds of millions of people. It can occur at any age from early childhood to late life. Dulling hope, ambition and sometimes even the will to live, depression exerts a tremendous cost upon society. Fortunately, the treatment of depression has advanced in recent years with the advent of drugs that block the inactivation of the brain neurotransmitters 5-HT and noradrenaline. One class of antidepressant drugs, the monoamine oxidase inhibitors, slows the normal enzymatic degradation of these neurotransmitters. Another class, the monoamine reuptake blockers, prevents the normal recapture of 5-HT and noradrenaline by their transport back into the presynaptic nerve-terminal. Selective reuptake blockers such as fluoxetine (Prozac) or desipramine thereby enhance levels of 5-HT or noradrenaline, respectively, in the nerve-terminal synapse. Other treatments for depression include electroconvulsive therapy (ECT), which is reserved for severely depressed patients who do not respond to conventional drug therapy. Yet, it has remained a puzzle as to why these diverse treatments are effective and why several weeks of antidepressant drug therapy or ECT are needed for a positive response.

Recent findings now suggest that antidepressant medications and ECT might work by boosting the production of the brain's own neurotrophic factors. Such actions could implicate deficiencies in endogenous neurotrophin production in depression, and suggest a 'neurotrophin-boosting' pharmacotherapy for depression that requires nerve growth for a clinical response.

### Neurotrophins: growth factors for 5-HT-containing neurones

Before the link between neurotrophins and depression was suspected, this family of growth factors had been studied for its role in the adult nervous system. Among these endogenous proteins, BDNF and NT-3 were shown to promote the function and growth of 5-HT-containing neurones in the adult brain. Unlike chronic infusions of nerve growth factor (NGF), chronic infusions of BDNF or NT-3 into the rat midbrain increased the turnover of 5-HT and levels of noradrenaline in many forebrain areas including the neocortex, basal ganglia and hippocampus[1–4]. More strikingly, infusions of BDNF into the adult rat neocortex produced an unprecedented and robust

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