Short and long loop nephrons

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The purpose of this article is to consider the question: what is the importance to the urinary concentrating mechanism of having nephrons with two different configurations? The question is important, since of the two types of nephron, only one has loops of Henle in the inner renal medulla, the region with the highest osmotic pressure. While a definitive answer is not yet available, several features are described which lay the basis for a speculative conclusion.

Classification

Nomenclature

Nephrons are designated either according to the position of their glomeruli in the cortex or to the lengths of their loops of Henle [1]. Three types of glomeruli and corresponding nephrons can be distinguished: superficial, midcortical, and juxtamedullary. Superficial glomeruli are located in the layers of cortex nearest the surface. Their efferent arterioles ascend directly to the surface. Juxtamedullary glomeruli are situated in the deepest layers of the cortex and give rise to efferent arterioles that descend directly into the outer medulla to form descending vasa recta. The remaining glomeruli, which represent the majority, are midcortical; their efferent arterioles are relatively short compared to those of the superficial and juxtamedullary glomeruli. Superficial and midcortical glomeruli are smaller than juxtamedullary glomeruli. (Some authors use the term cortical nephron interchangeably with superficial nephron, but the former more precisely designates a nephron whose entire loop of Henle is confined to the cortex. Since cortical nephrons are a minor component and do not participate in the concentrating mechanism, they will not be considered further.)

Nephrons are also classified as short or long loop nephrons. In most species all short loops descend to the same level, the innermost third of the outer medulla. The long loop nephrons are those with loops which penetrate the inner medulla. Their hairpin turns are found throughout the length of the inner medulla, but most loops turn in the superficial part of the inner medulla; the number of hairpin turns falls progressively toward the tip of the papilla. In the rat more than 80% of long loops of Henle turn back within the first half of the inner medulla. Of an estimated 10,000 long looped nephrons, only 1,500 reach the lower half of the inner medulla and about 250 reach the papillary tip. This exponential decrease in number of loops, the parallel

decline in number of vasa recta, and the progressive fusion of branches of the collecting duct, account for the tapered inverse–pyramid or cone–shaped form of the renal papilla found in most mammals.

Classification of nephrons by position of the glomeruli unfortunately doesn't coincide with classification according to length of Henle's loop [1, 2]. Juxtamedullary glomeruli regularly give rise to long loops of Henle except in a few species whose kidneys have only short loop nephrons. There are fewer juxtamedullary glomeruli, however, than long loop nephrons. For example, the rat has 30% long loop nephrons but only 16% juxtamedullary nephrons. In the rabbit 60% of the nephrons have long loops, but only 10% of glomeruli are juxtamedullary. Depending on the ratio of long to short loops, this means that some midcortical and occasionally even superficial glomeruli supply long loops.

It seems likely that the length of Henle's loop is more germane than the cortical location of glomeruli to the urinary concentrating mechanism. Accordingly, this review will employ the short and long loop nephron classification. Short loop nephrons have smaller glomeruli and longer partes rectae. Since the thick ascending limb becomes the distal convoluted tubule at the macula densa next to its own glomerulus, the more superficial the location of the glomerulus, the longer the cortical thick ascending limb. Thus, short loop nephrons have longer cortical thick ascending limbs than do long loop nephrons. The medullary thick ascending limb segments are generally of similar lengths in both short and long loop nephrons. Long loop nephrons have larger glomeruli, longer proximal convoluted tubules, shorter partes rectae, longer thin descending limbs and a segment not found in short loops, the thin ascending limb. The pars recta and thick ascending limb of long loop nephrons with midcortical glomeruli lie within the medullary ray, like the pars recta and thick ascending limb of short loop nephrons, whereas the analogous segments of long loop nephrons with juxtamedullary glomeruli are located in the cortical labyrinth.

Ratio of short to long loop nephrons

Most species studied thus far have both long and short looped nephrons. The ratio of short to long loop nephrons is estimated to be 97:3 in the pig, 85:15 in man, 75:25 in the mouse, 70:30 in the rat, 66:34 in the *Psammomys*, and 34:66 in the rabbit [2]. The few species whose kidneys have only short loops (mountain beaver, beaver, muskrat) have no inner renal medulla and their urinary concentrating ability is low. Conversely, the cat and the dog have only long looped nephrons. Their concentrating ability is average. The correlation between the ratio of short
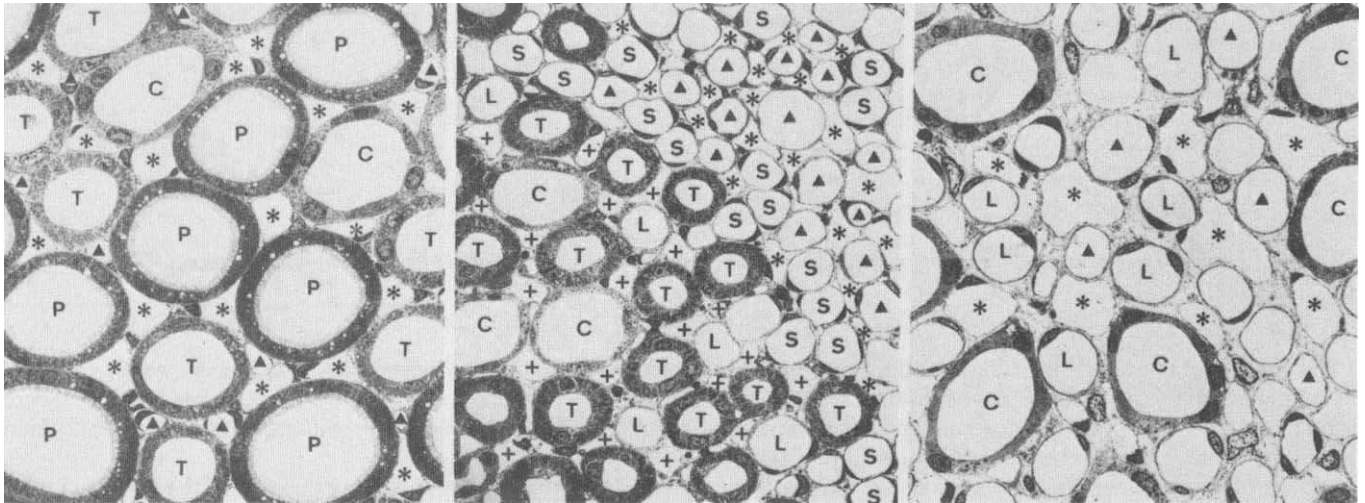
Fig. 1. *Electron micrograph of outer stripe and inner stripe of outer medulla and of inner medulla in cross sections.* Outer stripe is from a rabbit kidney, inner stripe and inner medulla are from a rat kidney. Bar ≈ 30 μm. Abbreviations are: P, pars recta; C, collecting duct; T, thick ascending limb; S and L, thin descending limbs of short and long loops, respectively. Symbols are: solid triangles, descending vasa recta; asterisk (*), ascending vasa recta, and +, extrabundle ascending vasa recta in the inner stripe. In the outer stripe, note the large area of contact between ascending vasa recta and pars recta and paucity of interstitial space. In the inner stripe, part of a vascular bundle is seen in upper right half of picture and an extrabundle region in lower left half. The extrabundle ascending vasa recta intermingle with collecting ducts, long descending limbs and thick ascending limbs. Ascending vasa recta outnumber descending vasa recta in the outer stripe and throughout the medulla. In the inner medulla there is more interstitium and less regional topography. In the outer stripe, the pars recta could exchange with ascending or descending vasa recta, the thick ascending limb and, to some extent, the collecting duct. In the inner stripe, primary opportunities for exchange, starting from the left side of the middle panel, are collecting tubule or thick ascending limb with extrabundle ascending vasa recta; descending thin limb of long loop with extrabundle ascending vasa recta and thick ascending limb; descending limbs of short loops with thick ascending limb, intrabundle ascending vasa recta or descending vasa recta; intrabundle ascending vasa recta with descending vasa recta. In the inner medulla, primary opportunities for exchange appear to be descending limb of long loop with ascending vasa recta and ascending vasa recta with descending vasa recta. From [2], used with permission.

to long loops and urinary concentrating ability is not very informative, except that in the most highly concentrating rodent species, the number of short loops is always greater than the number of long loops [2].

Morphology of thin limbs of Henle's loops

The thin limb segments of the loops of Henle can be subdivided according to cytological criteria [1]. The descending limb of the short loop has an epithelium which is flat and undifferentiated (designated TL_1 [1] or SDL for descending limb of short loop [3]). Descending thin limbs of long loops have an upper (TL_2 [1] or LDL_u, for upper portion of descending limb of long loop [3]), and a lower (TL_3 [1] or LDL_1 [3]) part. There are ultrastructural differences in TL_2 (or LDL_u) among species. In the rat, mouse or *Psammomys*, the upper part is characterized by heavily interdigitating epithelial cells with shallow, tight junctions, numerous mitochondria and many apical microvillae. In the rabbit and guinea pig, cells of the TL_2 epithelium don't interdigitate and the tight junctions are much deeper. The ultrastructure of the lower part (TL_3 or LDL_1) of the long descending limb is relatively simple and does not differ among species; cells do not interdigitate and tight junctions are relatively deep. A short distance before the bend of the loop, the epithelium transforms from TL_3 (LDL_1) to that of the ascending thin limb (TL_4 or TAL) segment and is distinguished by heavily interdigitating cells connected by shallow, tight junctions.

Renal topography and the concentrating mechanism

The location of the descending and ascending limbs of the loops of Henle distinguishes two groups of species. As illustrated in Figure 1 reproduced from Bankir and de Rouffignac's review [2], and summarized in Table 1, the outer medulla has a vascular–rich and a vascular–poor region. In the species with a *simple medulla*, the vascular–rich region contains a vascular bundle (ascending and descending vasa recta) that forms in the outer stripe of the outer medulla, is most prominent in the inner stripe, and gradually tapers in the upper portion of the inner medulla. In some species (such as the rabbit) the vascular–poor region (also called the interbundle region) contains all the renal tubules; the descending limb and thick ascending limb of the long loop are situated adjacent to the vascular bundle, next to them are the descending and thick ascending limb of the short loop, and next to them is the collecting duct. Those species with a greater urinary concentrating ability have a *complex medulla* which has a more complicated topography. The descending limb of the short loop swings over from the vascular–poor region to the vascular–rich region to descend alongside the vascular bundle (such as the rat), Figure 1, or actually within the vascular bundle (such as mouse). Near the junction of the inner stripe of the outer medulla with the inner medulla, the descending limb swings back to the region next to the collecting duct to form the beginning of the thick ascending limb of the short loop.

According to the principle of countercurrent exchange, flow

Table 1. Topography of the renal medulla

Level	Interbundle region					Vascular bundle
Inner cortex medullary ray only	Cortical collecting duct.	Thick ascending limb of short loop.	Pars recta (P3) of short loop.			None
		Ascending vasa recta derived from extra bundle region of outer medulla interspersed.				
Outer medulla outer stripe	Outer medullary collecting duct.	Thick ascending limb of short loop.	Pars recta (P3) of short loop.	Thick ascending limb of long loop.	Pars recta (P3) of long loop.	Efferent arterioles of deep glomeruli and their first branches give rise to descending vasa recta (DVR). Bundles of DVR and ascending (AVR) vasa recta begin to form.
inner stripe (simple medulla)	Outer medullary collecting duct.	Thick ascending limb of short loop.	Thin ascending limb (TL$_1$) of short loop.	Thick ascending limb of long loop.	Thin descending limb (TL$_2$) of long loop.	Descending and ascending vasa recta.
inner stripe (complex medulla)	Outer medullary collecting duct.	Thick ascending limb of short loop.	Thin descending limb (TL$_2$) of long loop.	Thick ascending limb of long loop.	Thin descending limb (TL$_1$) of short loop.	Descending and ascending vasa recta.
(both)		Extrabundle ascending vasa recta originating in inner stripe.				
Inner medulla	Inner medullary collecting duct.	Thin descending limb (TL$_3$) of long loop.	Thin ascending limb (TL$_4$) of long loop.			Descending and ascending vasa recta. Vessels not grouped together in lower inner medulla.
		Interstitum more prominent.				

in adjacent channels in opposite directions will maximize interchannel exchange, providing both walls are permeable to that which is to be exchanged (water or solute). Taking into account the topography of the medulla, Table 1 and Figure 1 indicate likely countercurrent exchange possibilities between channels, starting in the medullary ray and descending through the outer medulla and inner medulla to the papillary tip. Whether exchange of water or solute between adjacent channels actually occurs depends on the permeability properties of the adjacent channels and the presence of a driving force. For example, intercapillary transfer of globulin in the vascular bundle would not be likely to occur even though descending and ascending vasa recta are adjacent to each another, since their walls are believed to be essentially impermeable to globulin. On the other hand, it is highly likely that there is transfer of non-protein solutes like urea and salt from ascending to descending vasa recta. It is also probable that there is net movement of water from descending to ascending vasa recta, but the extent is not clear since the driving force depends on the capillary reflection coefficients and they are unknown.

Given the topographical location and structural differences between short and long loop nephrons and the central role that the loops play in the concentrating mechanism, why is it that both types of nephrons appear necessary for maximum urinary concentrating ability? The remainder of this article considers that question.

Phylogeny

The nephrons of most non-mammalian vertebrates lack loops of Henle and are arrayed perpendicularly to the collecting ducts [4]. This arrangement is not conducive to the production of a hypertonic urine nor is there any evidence that these animals excrete a hypertonic urine. Of great interest is the avian kidney because it contains both types of nephrons, non-mammalian and mammalian. Most avian nephrons (70 to 90%) are the non-mammalian type, which are located in a superficial region of the kidney, lack loops of Henle, and empty at right angles to the collecting duct. The remaining nephrons are mammalian in configuration and are located in the lower half of the avian kidney, a region that resembles the mammalian kidney topographically and has a long, tapering medullary cone containing short loops, long loops, vasa recta, and collecting ducts. An osmotic gradient in the medullary cone, corresponding to a urine–to–plasma osmolality ratio of 2.5, has been demonstrated. Most solute in the avian medulla is sodium chloride; urea comprises a very small component.

The length of the renal papilla, which is an index of the length of the longest loops, generally correlates with maximum con-
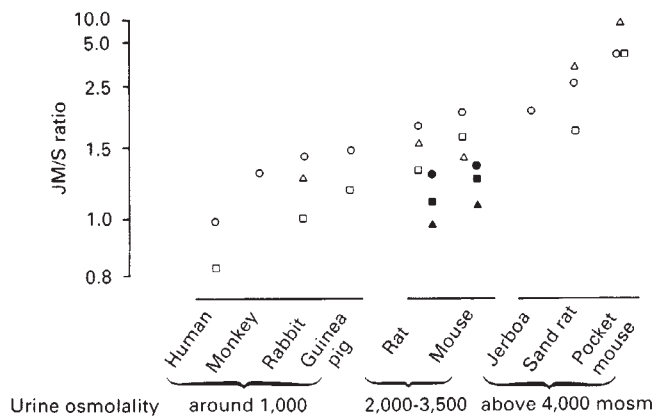
Fig. 2. *Heterogeneity of nephrons and urine concentrating ability.* Ratios of juxtamedullary over superficial nephrons (JM/S) (log scale) are shown for single-nephron filtration rate (generally determined by Hanssen's or modified Hanssen's technique) (triangles), for glomerular volume (circles), and for proximal tubular length (squares). Solid symbols, animals with hereditary diabetes insipidus. From [2], used with permission.

centrating ability of a given species, but there are exceptions, indicating that the length of papilla alone cannot entirely explain the capacity to excrete a highly concentrated urine. As depicted in Figure 2 [2], there is also a correlation of concentrating ability with the juxtamedullary–to–superficial ratios of glomerular volume, single nephron glomerular filtration rate (SNGFR), and length of proximal tubule. The pocket mouse, the animal that produces the most concentrated urine, has a ratio of juxtamedullary–to–superficial SNGFR of 10:1 [2]. Note, however, that these differences are a function of the cortical location of the glomerulus, not whether the nephron has a short or long loop. In the rat in chronic water diuresis owing to diabetes insipidus (the Brattleboro rat), the difference in SNGFR between superficial and juxtamedullary glomeruli is less than in normal rats but this is not associated with a change in the ratio of short to long loops of Henle, so far as is known.

In birds arginine vasotocin is the antidiuretic hormone. Although vasotocin may increase the permeability of the collecting duct to water, this effect has not yet been studied; it is known, however, that vasotocin acutely reduces the number of filtering reptilian–type nephrons and thus lowers the fluid flow reaching the collecting ducts, a factor that regulates urinary concentrating ability [4]. Normally, after a water load, all glomeruli in the quail, both mammalian and reptilian, are open and filtering. Vasotocin administration shuts off filtration in 3/4 of the reptilian nephrons and causes the SNGFR to fall by half in those nephrons which continue filtering.

Ontogeny

One is struck by the fact that maximum urinary concentrating ability at birth is modest, even though the total number of nephrons and their topographical relationship are approaching their final form. Studies of the thick ascending limb at various stages in its development, have shown that the capacity for ion transport in the thick ascending limb and the concentration of non-urea solute in the outer medulla and inner medulla rise in parallel [5]. Horster [5] suggests that the combination of the

increasing ion transport capacity of the thick ascending limb and the descent of the loops into the medulla to provide a greater diffusion area for medullary sequestration and recirculation of urea are key to the development of urinary concentrating ability.

It is important to emphasize that the volume of tissue to be osmotically concentrated falls exponentially from the cortical–medullary junction to the papillary tip, as illustrated in Figure 3 [2].

Integration

The foregoing considerations suggest optimal requirements for the urinary concentrating mechanism. First, it requires both short and long loops of Henle in a ratio about four or five to one, with the glomerular filtration rate being higher in the long loop than in the short loop nephrons. Second, the thick ascending limb in the outer medulla should have a large, active sodium–chloride transport capacity. Third, the thin descending limb of the short loop in the inner stripe of the outer medulla should translocate from a position peripheral to the vascular bundle to a location next to or within the bundle. Fourth, the solute sequestered in the inner medulla should consist of as much urea as sodium chloride.

As originally proposed by Kuhn, the loop of Henle acts as a countercurrent multiplier (*Vervielfaltigung Multiplikation*). Multiplication was not used by Kuhn to mean "to cause to become many" but to "augment" or "to increase," so a truer translation from the German would be "countercurrent augmentation" [1]. The three basic requirements of a countercurrent augmenter are: 1) adjacent channels with countercurrent flows; 2) difference in permeability of the channel walls; and 3) a source of energy. Evidence that the thick ascending limb of Henle fulfills these three requirements is strong [1]. It is adjacent to the descending thick (pars recta) or thin limb and to descending vasa recta (Fig. 1). It is impermeable to water and has a variable permeability to solute, while the adjacent descending channel (the pars recta or descending limb) is highly permeable to water and variably permeable to solute. Finally, the thick ascending limb has an internal source of energy generated by the active transport of sodium chloride from the lumen to the interstitium which creates the essential transepithelial difference in osmotic pressure (the Einzeleffekt or single effect).

In contrast, the thin loop of Henle meets only two of the three requirements of a countercurrent augmenter. The thin ascending limb lies close to the thin descending limb and to descending vasa recta. It is impermeable to the osmotic–induced flow of water but highly permeable to ions, while in contrast the thin descending limb is highly permeable to water but, at least in the rabbit, is poorly permeable to ions and urea. There is no compelling evidence, however, that the thin ascending limb has an active transepithelial transport mechanism. Yet the contents of the thin ascending limb are hypo-osmotic to the interstitium, that is, the thin ascending limb generates the single effect [1]. So a search continues for a mechanism that satisfies the third requirement, an energy supply in the inner medulla. The prevailing theory is that a concentrated solution of urea is passively reabsorbed from the inner medullary collecting duct and, in the process of being diluted in the inner medullary interstitium by the addition of solute–free water from the thin
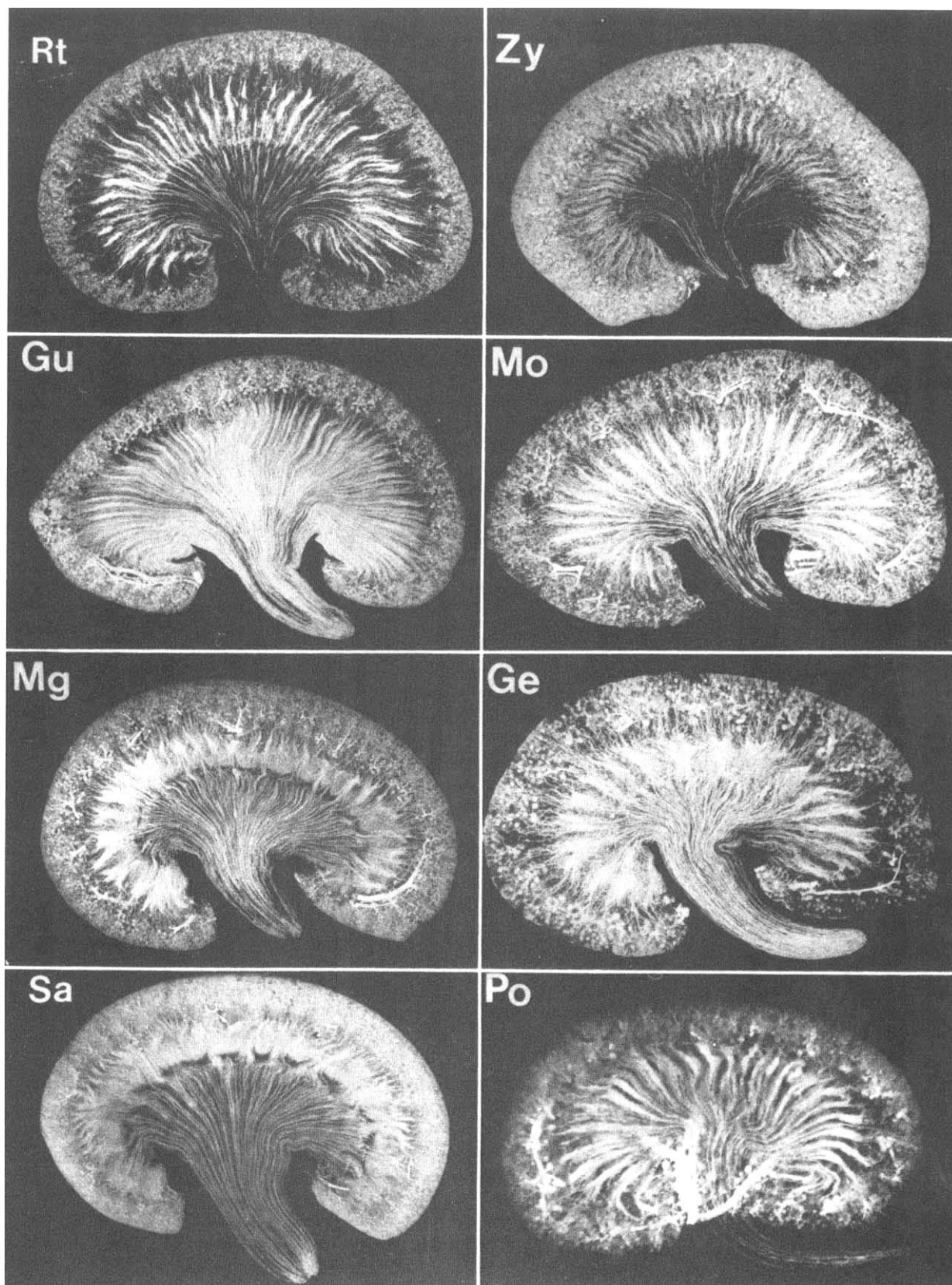
Fig. 3. *Midsagittal sections of kidneys of various rodents injected with microfil.* Abbreviations are: Rt, rat; Zy, Zygodontomys; Gu, gundi; Mo, mouse; Mg, Mongolian gerbil; Ge, gerbil; Sa, sand rat; and Po, pocket mouse. Enlargement of each picture has been adapted to facilitate comparisons; the size of kidneys varies widely. The mass of medullary tissue to be concentrated decreases and the tissue osmolality rises exponentially to the papillary tip. Note short papilla in rat and Zygodontomys and very long extrarenal papilla in gerbil and pocket mouse. From [2] used with permission.

descending limb, transfers energy to the thin ascending limb by concentrating sodium chloride in the tubule fluid to a level higher than the sodium chloride concentration in the interstitium. Passive diffusion of sodium chloride across the thin ascending limb down the concentration gradient thus established creates the essential single effect [6, 7].

Thick ascending limb

NaCl reabsorption. As described elsewhere in this issue [8, 9], the thick ascending limbs of short and long loop nephrons have the right combination of transport and permeability properties to serve as a countercurrent augmenter. These properties (and general references) are summarized in Table 2. The thick ascending limb (both medullary and cortical segments) has an extremely low hydraulic conductivity. The sodium permeability of the rabbit medullary thick–ascending–limb is about twice that of the cortical thick ascending limb and approximately equal to the sodium permeability of the pars recta. The chloride permeability is one–half to one–sixth of the sodium permeability. The net flux of sodium across the medullary thick ascending limb in vitro, 16 to 40 $\times$ 10^{12} mol cm^{-1} sec^{-1}, is three times greater than that across the cortical thick ascending limb, and so is the net chloride flux. On the other hand, the cortical thick ascending limb can reduce the sodium chloride concentration in the luminal fluid to a lower value. Thus, the medullary thick ascending limb has the greater NaCl transport capacity, but is a leakier epithelium and cannot reduce the luminal salt concentration to low levels, whereas the cortical thick ascending limb has a lower NaCl transport capacity but is less leaky and can reduce the luminal salt concentration to a low value.

Evidence strongly suggests that the thick ascending limb has a load–dependent reabsorptive capacity. The membrane transport mechanisms underlying this capacity have been examined by several investigators [8, 9]. A carrier located in the luminal membrane requires one sodium, two chloride and one potassium ion, and is driven by the electrochemical transmembrane sodium gradient. Sodium in the thick ascending limb cell is expelled to the interstitium by sodium–potassium activated ATPase in the basolateral membrane. The higher capacity for salt transfer of the medullary thick ascending limb is presumably a function of the number of carriers on the luminal membrane and the amount of ATPase in the basolateral membrane.

Reabsorption of NaCl increases the NaCl concentration of the interstitium surrounding the thick ascending limb. This will extract water from descending limbs of all nephrons, and may also create a driving force for the net addition (secretion) of NaCl from the interstitium into the descending limb of the long loops (TL$_2$ segment), but not of the short loop nephron because the latter's descending limb (TL$_1$) is not permeable to salt and has a very high reflection coefficient to NaCl (Table 2). In rodents with a complex medulla, moreover, only descending limbs of long loops lie near the thick ascending limbs (Fig. 1, Table 1). The consequence of water extraction and possible NaCl secretion is to reduce the volume flow of water in all descending limbs and (possibly) increase the mass flow of NaCl in the descending limbs of long loops.

As first shown by Hall and Varney [12] and subsequently confirmed by others [6, 7], antidiuretic hormone stimulates sodium chloride reabsorption by the medullary thick ascending limb, which achieves the effect of adding more sodium chloride to the outer medulla to counteract the dilution which follows the ADH-induced increase in water reabsorption in the outer medullary collecting duct. It also may result in the increased mass flow of NaCl in the TL$_2$ segment of the descending limb of the long loop nephrons by means of secretion.

Urea reabsorption. Knepper [11] has shown that the thick ascending limb in the outer medulla has a lower permeability to urea, 0.75×10^{-5} cm sec^{-1}, than the thick ascending limb in the medullary ray (lower section of cortex) (1.4) or in the cortex (2.0) (Table 2). Fluid entering the thick ascending limbs of short and long loop nephrons, especially the latter, is rich in urea as a consequence of transepithelial addition of urea in the pars recta and thin loop of Henle. Urea is likely to be passively reabsorbed in the thick ascending limb, especially from the medullary ray and cortical segments of the thick ascending limb of the long loop nephron. To the extent that reabsorption of urea free of water occurs in the thick ascending limb in the outer medulla or medullary ray, water is separated from solute (single effect), contributing simultaneously to the hypertonicity of the outer medulla and hypotonicity of the luminal fluid [11]. The advantage of urea reabsorption in the cortical thick ascending limb is less obvious. Some have argued that as long as the reabsorbed urea re-enters the short loop of Henle (via the pars recta) and is thereby captured for delivery to the inner medullary collecting duct, there is no disadvantage to urea reabsorption in the cortical thick ascending limb. But if trapping urea for delivery to the collecting duct is desirable, it would be even better to have a urea–impermeable cortical thick ascending limb. The solution to this paradox may lie in the substantial difference between mass flows of urea in the short and long loop nephrons. In an adult rat, for example, the mass flow of urea entering the thick ascending limb of the short loop is about 110% of the filtered load (single nephron glomerular filtration rate [SNGFR] of the short loop nephron $\times$ plasma urea concentration), 1.1 [(35 nl/min) $\cdot$ (7 pM/nl)] = 270 pM/min. In contrast, the mass flow of urea reaching the thick ascending limb of the long loop is more than six times the filtered load, 6 [(50 nl/min) $\cdot$ (7 pM/nl)] = 2100 pM/min. Since the tubule fluid flow rate leaving the thick ascending limb of the long loop is likely to be less than 10 nl/min, the urea concentration of fluid entering the distal convoluted tubule must be greater than 210 pM/nl, that is, >210 mM/liter or >210 mOsm/liter. An estimate of the total osmolality of the tubule fluid is obtained by adding to that urea contribution 100 mOsm/liter to account for the minimum concentration of NaCl (50 mM/liter) and 25 mOsm/liter for the concentration of all other solutes. The calculated total osmolarity is >335 mOsm/liter. Therefore, unless urea is reabsorbed by the thick ascending limb of the long loop, fluid entering the distal convoluted tubule of the long loop nephron will be hyperosmotic to fluid entering the descending limb, which would dissipate the hyperosmotic medullary interstitium.

Thus, a combination of the topographic location of the thick ascending limb and pars recta and their permeability properties appears to facilitate the net transfer of urea from the thick ascending limb of long loop nephrons to the pars recta of short loop nephrons, and thereby returns urea to the collecting duct to complete the cycle.

Thin descending limb

The permeability and transport properties of the thin loops of Henle are summarized in Table 2 [3]. As noted above in species with a high urine concentrating ability, in the inner stripe of the complex medulla, the thin descending limb (TL$_2$) of the long loop is surrounded by thick ascending limbs of short and long loops, while the thin descending limb of the short loop is adjacent to or within the vascular bundle (Fig. 1). The urea permeability of the descending limb (TL$_1$) of the hamster short loop nephron is high—five times as great as the urea permeability of the descending limb of the rabbit short loop (Table 2). In contrast, the urea permeability of the proximal portion of the descending limb (TL$_2$) of long loops is the same in rabbit and hamster. From these characteristics one can deduce that fluid in the short loop of the complex medulla is enriched by urea addition at two sites: the pars recta (urea supplied from the cortical thick ascending limb) and the descending limb (from ascending vasa recta loaded with urea from the inner renal medulla). That accounts for the fact that in the short loop nephrons mass flow of urea to the beginning of the distal convoluted tubule is substantially higher than the flow of urea leaving the proximal convoluted tubule.

To recapitulate, in species with a complex medulla urea recycles from ascending vasa recta to the descending limbs of short loop nephrons. Urea also recycles from the cortical thick ascending limb of long loop nephrons into the pars recta of short loop nephrons.

The sodium permeability of the proximal segment of the long descending limb (TL$_2$) of the hamster is extremely high, 45 × 10^{-5} cm sec^{-1}, an order of magnitude higher than the sodium permeability of any other segment of the nephron except the thin ascending limb [3] (Table 2). Similarly, the potassium permeability is also high. Considering the immediate neighbors of TL$_2$, it is possible that solute cycling occurs into the TL$_2$ in the outer medulla: sodium from the thick ascending limb and potassium from the collecting duct. The evidence for sodium cycling is not unequivocal but very suggestive [1]. (The evidence for potassium cycling is unequivocal [13], but is beyond the scope of this article.) de Rouffignac and Morel showed that the mass flow of sodium at the end of the long descending limb in the *Psammomys*, an animal with a complex medulla, is a function of the hypertonicity of the medulla and rises to values equalling (but not exceeding) the filtered load, a finding repeatedly confirmed [14]. Jamison and his colleagues [15], on the other hand, could find little evidence for sodium cycling in the Brattleboro rat, a strain which lacks antidiuretic hormone. The delivery of sodium to the end of the descending limb did not change significantly between water diuresis and antidiuresis, which led them to infer that water extraction was the principal mode of concentration of the contents of the descending limb in a Brattleboro rat. The findings were considered consistent with the passive model of Hogg and Kokko [7] which was based on the very low permeability to sodium and urea of the rabbit descending limb. Very recently, however, Pellai and Kokko [16] have reported preliminary findings in the normal rat that are consistent with (although they do not unequivocally prove) the thesis that large doses of ADH cause chloride cycling from the ascending to the descending thin limb of long loop nephrons. Conversely, de Rouffignac and his colleagues, as discussed in

this issue [17], have obtained data demonstrating that physiological doses of ADH given to Brattleboro rats chronically repleted with ADH reduce the delivery of sodium chloride to the end descending limb of long loops. Indeed, a mathematical model of profiles of water, sodium, potassium and urea transport along the descending limb of the long loop nephron [3, and personal communication from M. Imai] predicts sodium *reabsorption* from the TL$_2$ of the long loop nephron, because urea extracts water from the proximal descending limb, raising the luminal salt concentration above the salt concentration of the outer medullary interstitium.

Thin ascending limb

The thin ascending limb (TL$_4$) in all species studied has the same characteristics—a very low hydraulic conductivity and a very high permeability to sodium and chloride [3]. It also has a moderate urea permeability, in accord with which is the evidence that urea diffuses into the first millimeter of the thin ascending limb in vivo [1]. Whether a transepithelial outward gradient for sodium chloride from the thin ascending limb [1] exists throughout its entire length in the inner renal medulla so that a purely passive mechanism for NaCl reabsorption would suffice is unknown. Net addition of urea to the thin ascending limb would be expected to dissipate the transepithelial osmotic pressure difference. The advantage to the concentrating mechanism of urea diffusion into the thin ascending limb is not clear unless subsequent urea diffusion out of the thick ascending limb in the medullary ray contributes to further dilution of the luminal fluid, as suggested by Knepper [11]. But if urea delivery to the interstitium of the medullary ray were all that the long loop nephrons contributed, then one could ask why a kidney containing only short loop nephrons—like that of the muskrat does not concentrate as well as one with both short and long loop nephrons.

It may be that there is some as yet poorly understood interaction among the long loops in the inner medulla which confines urea entry to the initial segment of each thin ascending limb, allowing the fluid in the thin ascending limb to remain hypo-osmotic. Alternatively, the inner medullary collecting duct may be a source of energy, as suggested by Chandhoke and colleagues [18]. In the meantime, the machinery of the inner medulla goes on concentrating the inner medulla, oblivious of our ignorance.

Layton [19] has recently examined the role of the two types of nephrons in the concentrating mechanism. He begins by describing a simple mathematical model for a single nephron and then extends it to a multinephron model which incorporates a decreasing loop population as a function of increasing medullary depth. If all loops turn at the same depth, maximum urinary concentrating capacity is limited to e, the base of natural logarithms, times the plasma osmolality. In contrast, a decreasing loop population as a function of depth in the medulla beyond the outer–inner medullary junction greatly enhances the concentrating ability. The key assumptions in Layton's model are: 1) NaCl is actively reabsorbed throughout the ascending limb, both thick and thin segments; 2) the descending limb, distal convoluted tubule and collecting duct are permeable to water but not to solute; and 3) solute supplied to the interstitium by reabsorption from the ascending limb extracts water from the descending limb and the collecting duct according to the

Table 2. Permeability and transport characteristics of segments of the short and long loop nephrons and collecting ducts determined in vitro

Segment	L_P (10^{-5} cm^3 cm^{-2} atm^{-1} sec^{-1})	Permeability (10^{-5} cm sec^{-1}) H$_2$O	Na	Cl	Urea	K	Reflection coefficient (σ) NaCl	Urea	KCl	Net flux (10^{-12} M cm^{-1} sec^{-1}) Na	Cl	Urea	K	Permeability ratios P_{Na}/P_{Cl}	P_K/P_{Cl}	References
Pars recta																
P$_3$s rabbit	21				1.7	1.0				8			−29	0.5–0.7		(3, 1, 10)
rat (no data)																
hamster (no data)																
P$_3$l rabbit			5.8	2.1	1.5	5.2				8			−48	1.3–2.0		(1, 11)
rat (no data)																
hamster (no data)																
Descending limb																
TL$_1$ rabbit[a] (or SDL) rat	15		1.6		1.5	2.5–4.0	0.96	0.95	0.96					0.75 / 0.61	1.19 / 1.02	(3, 10)
hamster	20		4.2	1.3	7.4									0.68	1.09	
TL$_2$ rabbit (see TL$_3$) (or LDL$_u$) rat														0.76 / 5.03	1.42 / 3.27	(3, 1)
hamster	29		45	4.2	1.5	58	0.83	0.95	0.81					3.98	4.90	
TL$_3$ rabbit (or TL$_2$) (or LDL$_1$) rat (no data)	27		1.6		1.5	4.0	0.96	0.95	0.96							(1)
hamster (no data)																
Thin ascending limb																
TL$_4$ rabbit (or TAL) rat	0.1	50	26	117	6.7	26				0				0.29	0.28	(1, 10)
rat	0.2		80	184	23	80								0.43	0.52	
hamster	0.2		88	196	18.5	88								0.38	0.49	
Thick ascending limb																
cortical rabbit			2.8	1.4	2.0					13	7–10					(1, 10)
rat														2.7		
hamster (no data)																
medullary rabbit	0		6.3	1.1	1.4 (OS) / 0.75 (IS)	0.7				16–40	16–18			5.9		[1, 8]
rat										10	21			1.86	3.27	
hamster														2.30	2.64	
Collecting duct, no ADH[b]																
cortical rabbit	0–0.1		0.1	2.1–4.7	0–1	1–1.5				3.8–5.7	0.5	−2.0 to −15				[1, 10]
rat (no data)																
hamster (no data)																
outer medullary rabbit			0.4	0.5	0.3	0.6				0	0	0				[1, 10]
rat (no data)																
hamster (no data)																
inner medullary rabbit			0.9	1.2	2.0	4.0				1.8	3.6	3–10				[1, 10]
rat	0.3	45	5.4		14–20											
hamster (no data)																
Collecting duct, with ADH[b]																
cortical rabbit	1.2–2.8															[1, 10]
rat (no data)																
hamster (no data)																
outer medullary rabbit	1.5															[1, 10]
rat (no data)																
hamster (no data)																
inner medullary rabbit	0.5				2.0											[1, 10]
rat	2.0	87	5.9		30–36					0.9	0.4					
hamster (no data)																
Proximal convoluted tubule[c]																
superficial P$_1$s rabbit			2.1	5.5		4.8	0.9			24				>1		[10]
rat			2.1	16		19										
hamster (no data)																
P$_2$s rabbit	16–39									24				2		[10]
rat (no data)																
hamster (no data)																
juxtamedullary P$_1$l rabbit			2.3	5.6		1.4				14				<0.5		[10]
rat (no data)																
hamster (no data)																
P$_2$l rabbit										14				2		[10]
rat (no data)																
hamster (no data)																

[a] Not sure if TL$_1$ or TL$_2$

[b] Evidence incomplete for ions but ADH increases L_P and P_{urea}

[c] Included in table to allow comparison with loop segment characteristics

Abbreviations are: L_P, hydraulic conductivity; P_{Na}, P_{Cl}, P_K, P_{urea}, permeability to sodium, chloride, potassium and urea, respectively; P$_1$s, P$_2$s, P$_3$s, first, second and third segments of the proximal tubule of the short loop nephron, respectively; P$_1$l, P$_2$l, P$_3$l, first, second, and third segments of the proximal tubule of the long loop nephrons, respectively; TL$_1$, thin descending limb of short loop (also abbreviated SDL); TL$_2$, proximal segment of the thin descending limb of long loop (also abbreviated LDL$_u$); TL$_3$, distal segment of the thin descending limb of long loop (also abbreviated LDL$_1$); TL$_4$, thin ascending limb (also abbreviated TAL); ADH, antidiuretic hormone; IS, inner stripe; and OS, outer stripe of outer medulla.

relation, $C = J_{2S}/J_V$, where at a given location in the medulla, C is the local interstitial osmolality, J_{2S} is the amount of NaCl reabsorbed from the ascending limb, and J_V is the volume of water reabsorbed from the descending limb. The reabsorbed water and solute are picked up by the vasa recta capillaries. The concept of the model is that the shorter loops preconcentrate the fluid in the descending limb of the longer loops. The latter in turn deliver all the solute to the thin ascending limb where maximum solute reabsorption is confined to the region traversed only by the longer loops, that is, the inner medulla. This produces a "cascade" effect and concentrates the inner medulla much more than in the model where all loops turn at the same level.

It is impressive that according to Layton's model the decline in number of long loops as a function of depth in the inner medulla of the rat is nearly optimal. If the decline in number of long loops is too rapid, then the presence of nonreabsorbable solute in the collecting duct along with its obligated water impairs the concentrating ability near the tip. If the decline in loop population is too slow, the cascade effect is lost. It remains to be determined how well Layton's model works when it incorporates a passive mechanism for NaCl reabsorption in the thin ascending limb.

Summary

The explanation for the necessity to have both short and long loop nephrons for urinary concentration is unknown but may represent nature's resolution of conflicting ideal conditions for maximum urinary concentration. Ideally, one would like the thick ascending limb to extend throughout the entire medulla to the papillary tip and be supplied by a blood flow vigorous enough to provide oxygen and remove waste products as rapidly as needed. One would also like to have a progressively smaller volume of tissue to be concentrated toward the papillary tip to lessen the osmotic work required (Fig. 3) and a highly efficient vascular exchange system to sequester the medullary interstitial solute effectively (Fig. 1). But the same efficiency of countercurrent exchange of oxygen causes the inner medulla to have a relatively low oxygen content [1].

The presence of the thin loops of Henle in the inner medulla may represent a compromise between these conflicting ideals. The papilla tapers to a low mass, which allows a mechanism requiring only a modest energy supply to increase the tonicity of the interstitium enormously. The reduced work requirement obivates the need for thick ascending limbs to extend into the papilla where they would be highly vulnerable to anoxia [20]. The outer medulla with its larger mass and thick ascending limbs supplied by a high blood flow can initiate the operation to reduce the volume of fluid and solute to be concentrated, and at the same time carry out other functions required of the filtration–reabsorption kidney.

Finally, a new mathematical model has demonstrated that a higher medullary interstitial osmolality can be reached by the coupling of one set of nephrons, that all turn at the same level, with a second set of nephrons, which exhibit a continuously decreasing loop population as a function of increasing medullary depth.

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