# COUNTERCURRENT TRANSPORT IN THE KIDNEY<sup>1</sup>

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### INTRODUCTION

Renal physiologists recognized many years ago that the ability of a glomerular kidney to form a concentrated urine was correlated in some way with the possession of a loop of Henle (see 56). It was also recognized that more water than solute must be absorbed from the glomerular filtrate to produce a urine more concentrated than plasma. Smith (62, 63) quantitated the relative water reabsorption by noting that if the final urine were to be reduced to isotonicity by the addition or subtraction of water, the total solute excreted by the kidney per minute would occupy a volume of  $UC_M/C_{pM}$ , where U is the urine flow,  $C_M$  is the urine osmolality, and  $C_{pM}$  is the plasma osmolality. Since the actual volume occupied by this solute is U, the quantity of water  $U = UC_M/C_{pM}$  would have to be subtracted when the urine is hypotonic and added when the urine is hypertonic to bring the final urine to isotonicity. Smith called this virtual volume free water for the diluting kidney and negative free water for the concentrating kidney. Since the micropuncture studies of Richards and his associates had shown that the glomerular filtrate was isotonic and remained so in the proximal tubule (57, 58), it was inferred that in the concentrating kidney the absorption of water in excess of its isotonic complement of solute took place somewhere in the distal nephron. For many years the mechanism of this distal water reabsorption remained totally obscure. It was suggested that it was by "active" water transport, but this concept turned out to be thermodynamically unsound (5). At last, in a series of brilliant papers, Kuhn and his co-workers implicated the medullary counterflow system (13, 38-40). Analyzing analogous counterflow systems theoretically and experimentally, they pointed out that counterflow permitted a small single membrane effect to be multiplied manyfold to produce a highly concentrated fraction of the outflow.

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Figure 1 Kuhn-type solute cycling multiplier. Black arrows, solute movement; white arrows, volume flow. If  $f_T$  is the fraction of solute recycled and  $f_U$  is the fractional withdrawal at the tip, then the concentration ratio developed by the system is  $r = 1/[1 - f_T(1 - f_U)]$ .

Kuhn's model, in a form that became widely accepted, is shown in Figure 1. Salt is actively transported from ascending Henle's limb to descending Henle's limb and collecting duct. Theoretical analysis of this model predicts a concentration gradient that increases from corticomedullary border to the tip of the papilla and high osmolality of all tip structures. These predictions were confirmed by slice and micropuncture studies (12, 42, 80, 83–85, 87). In this model, however, in the concentrating kidney there must be either net water addition to the loop of Henle or net solute addition to the collecting duct. Experimentally neither is found. In fact, micropuncture data show that in both the concentrating and diluting kidney there is net absorption of both water and solute from the nephron, with the water coming primarily from collecting duct and descending limb of Henle and the solute primarily from ascending limb of Henle; mass balance requires that this solute and water be exactly taken up by the vasa recta. This conservation requirement is entirely ignored by the Kuhn models.

Several years ago we introduced an alternative model of the concentrating mechanism (Figure 2) in which the basis of the theoretical analysis is the conservation relations between nephrons and vasculature (64–66). In this model and its more sophisticated successors, the basic medullary process is viewed not as solute cycling from ascending flow to descending flow, but volume absorption of descending flow driven by solute transport from ascending flow; and the basic concentrating unit is not the nephron, but an integrated nephrovascular unit consisting of loop of Henle, vasa recta, collecting duct, and distal cortical nephron.

It is in terms of this model that we analyze the mammalian concentrating mechanism, but in this review we derive the model by considering how folding the primitive straight glomerular nephron into an S-shaped counterflow system confers the ability to concentrate. This exercise gives considerable qualitative insight into various permeability requirements of the system. We then consider more quantitative insights that have been obtained from more detailed theoretical analysis and numerical calculations. Our emphasis in this review is on the theoretical analysis. We call the readers' attention to several excellent recent reviews that supplement our rather sharply focused review (3, 6, 21, 22, 44, 86).



Figure 2 Central core model of the renal medulla. (a) Salt ( $\Rightarrow$ ), water ( $\Rightarrow$ ), and urea ( $\Rightarrow$ ) movement in two-dimensional representation. With sufficiently high salt, water, and urea permeabilities of AVR and DVR, they functionally merge with the interstitial space into a single tube (CORE), closed at the papillary end, open at the cortical. Note that AHL is impermeable to water but permeable to salt and urea, and that DHL and CD are permeable to salt, water, and urea. (b) Shows (a) being rolled up like a bamboo curtain to give the final cross-section configuration of (c). The basic process going on in the system is that salt from AHL drives volume absorption from DHL and CD. This generates a net upflowing solution in the core that equilibrates osmotically with the downflowing fluid in DHL and CD. The concentration ratio generated is  $r=1/[1-f_r(1-f_u)(1-f_w)]$ . Where  $f_r$  is fractional AHL solute transport,  $f_u$  is fractional urine flow, and  $1-f_w$  measures the efficiency of countercurrent exchange [reprinted from Kidney International (64)].

# LOOPING THE NEPHRON TO CONCENTRATE

Absorbing more solute than water from the nephron to produce a dilute urine presents no great problem—given the ability of the tubular cells to transport salt against an electrochemical gradient. Let us consider a segment of tubule with transmural solute transport  $J_s$  and transmural volume transport  $J_v$ , per unit length. In the steady state and with negligible axial diffusion of solute, the luminal concentration  $C_L$  and the axial volume flow  $F_v$  obey the two conservation equations

$$\frac{dC_L}{dx} = \frac{J_v}{F_v} (C_L - J_s/J_v)$$
 1.

and d

$$\frac{dF_v}{dx} = -J_v. \tag{2}$$

The concentration of solute  $C_A$  in the absorbate is  $J_s/J_v$ . In the absorbing kidney with  $J_s$  and  $J_v$  both positive, it is obvious from equation 1 that if  $C_A > C_L$ , concentration along the tubule will decrease; conversely, if  $C_A < C_L$  then tubular fluid will be concentrated as it flows down the tubule. To integrate equations 1 and 2, we need phenomenological equations for  $J_s$  and  $J_v$ . Momentarily, in a simplification of the usual phenomenology of Kedem & Katchalsky (27), we will assume  $J_v$ depends only on osmotic forces and that  $J_s$  is proportional to luminal concentration; thus,

$$J_v = L_P \left( C_l - C_L \right) \tag{3}$$

and

$$J_s = a C_L, \qquad 4$$

where  $L_P$  is a hydraulic permeability coefficient, *a* is a pump constant, and  $C_I$  is the concentration in the interstitium (or bath for an experimentally isolated tubule) surrounding the tubule. On substitution of these phenomenological relations into equations 1 and 2, we obtain

$$\frac{dC_L}{dx} = \frac{C_L[L_p(C_I - C_L) - a]}{F_v}$$
5.

and

$$\frac{dF_v}{dx} = -L_p (C_l - C_L).$$
6.

Equation 5 can be formally integrated to give

$$C_{L}(x) = C_{L}(0) \exp \int_{0}^{x} \left[ \frac{I_{q}(C_{l} - C_{L}) - a}{F_{v}} \right] dx.$$
 7.

From equation 7 it is obvious that as long as  $F_v$  is positive, fluid entering the tubule will increase or decrease in concentration depending on the sign of  $L_P(C_I - C_L) - a$ . In any case, both the luminal fluid and absorbate tend toward the limiting concentration

$$C_L = C_l - a/L_p = C_A,$$

and volume absorption tends toward the limiting rate

 $J_v = a$ .

This simple phenomenology gives a reasonable qualitative description of salt and water transport in the primitive glomerular kidney (Figure 3). The nearly isotonic filtrate enters the proximal tubule where solute is actively transported to lateral intercellular channels (8, 15, 59, 61). Here a large hydraulic permeability of tight junction and/or basal lateral surface permits water to move from lumen to channel with only very small driving forces (59). The net result is a reabsorbate that is isotonic relative to luminal fluid and slightly hypotonic relative to the interstitial fluid. Detailed modeling shows that the channel itself is nearly in diffusive equilibrium with the surrounding interstitium (15, 16, 59). Recent measurements in isolated rabbit tubules are consistent with these theoretical concepts and suggest driving forces of the order of 1–4 mOsmol/liter can account for proximal absorption (60).

In the absence of a loop of Henle, *PT* fluid enters the diluting segment. Here a relatively water-impermeable wall results in the production of a fluid markedly hypotonic relative to the surrounding interstitium. Finally the fluid enters a segment in which the hydraulic permeability is under the control of the antidiuretic hormone (ADH) vasopressin. In response to this hormone the permeability of the final segment increases, thereby permitting the dilute fluid that enters the final segment to equilibrate osmotically with the surrounding interstitium. In the absence of ADH, the hypotonic fluid that leaves the diluting segment emerges as final urine. With this kidney, amphibians can produce a urine that varies from dilute to isotonic.

The primary problem that had to be solved in the evolution of the mammalian



Figure 3 The primitive three-section glomerular kidney. With its straight configuration solute and water transport from different segments is uncoupled. In the proximal tubule with a large effective hydraulic permeability  $L_p$ , absorption is nearly isotonic; in the diluting segment (DIL), a smaller  $L_p$  limits water absorption relative to solute and tubule fluid is diluted; in the final segment, hydraulic permeability is under the control of ADH. In the absence of ADH, tubule fluid remains dilute and in the presence of ADH it equilibrates with the surrounding interstitium. Thus final urine can vary from markedly hypotonic to isotonic relative to plasma.

8.

9.

kidney was how, given the basic configuration of the primitive kidney and its basic transport capabilities, i.e. active salt transport, variable salt permeability, and variable hydraulic permeability, can a kidney be made to concentrate? The answer, make a loop, although it eluded renal physiologists for many years, was progressively discovered by the kidney in its evolutionary course. This is because any loop that juxtaposes diluting and ADH-sensitive segments will result in some increase in concentrating ability and affords some adaptive advantage in a waterlimited environment.

The essential functional novelty introduced by the S-shaped configuration of the mammalian kidney (Figure 4) is that it permits salt from the diluting segment to extract water from the ADH-sensitive segment. Thus, salt from ascending limb of Henle (AHL) is deposited in the interstitium surrounding the collecting duct (CD). This solute raises the concentration of the solute in the interstitium above



Figure 4 The S-shaped mammalian kidney. The essential functional feature that allows concentration of urine is the juxtaposition of the diluting segment and the ADH-sensitive segment. This permits solute supplied by AHL to extract water from CD (and DHL). The net water extracted,  $T_{H_20}$ , equals  $T_s (1 - f_w)/C_{pM}$ , where  $T_s$  is net solute absorption from the medullary nephrons,  $C_{pM}$  is plasma osmolality, and  $1 - f_W$  is the exchange efficiency of the coupled nephrovascular counterflow system.

isotonicity and so osmotically extracts water from the water-permeable CD and renders the final urine hypertonic. If the CD is solute impermeable, then concentration of the final urine depends solely on the total water,  $T_{\rm H_20}$ , removed from the CD system. Thus, if  $F_{\rm CD}(0)$  and C(0) are the volume flow and concentration of fluid entering the CD and  $F_{\rm CD}(L)$  and C(L) are the volume flow and concentration of fluid leaving the CD as final urine, then mass conservation requires

$$F_{\rm CD}(0) \ C(0) = F_{\rm CD}(L) \ C(L).$$
 10.

The concentration ratio, r, of final urine-to-fluid entering the CD is then given by

$$r = \frac{C(L)}{C(0)} = \frac{F_{\rm CD}(0)}{F_{\rm CD}(L)} = \frac{F_{\rm CD}(0)}{F_{\rm CD}(0) - T_{\rm H_20}} = \frac{1}{1 - T_{\rm H_20}/F_{\rm CD}(0)}.$$
 11.

The problem of concentrating urine thus reduces to the question of how much water can be extracted from the CD system with a given amount of solute supplied by the AHL system. Not all of this solute from AHL is available to extract water from the CD. Part of it is lost by vascular "washout," and part of it either extracts water from descending limb of Henle (DHL) or leaks back into it to be recycled. The efficiency of the system is further limited by failure of the CD and DHL to equilibrate completely with the surrounding interstitium. We consider each of these in turn.

# NEPHROVASCULAR COUPLING

In the steady state, solute and water absorbed from the medullary nephrons must exactly equal water and solute removed from the medulla by the vasa recta and associated capillaries. Thus, we have the two balance requirements

$$T_{\rm H_{2}0} = F_{\rm AVR}(0) - F_{\rm DVR}(0) = \Delta F$$
 12.

and

$$T_s = F_{AVR}(0) \ C_{AVR}(0) = F_{DVR}(0) \ C_{DVR}(0),$$
 13.

where  $F_{\text{DVR}}(0)$  and  $C_{\text{DVR}}(0)$  are the volume flow and concentration of fluid entering the descending vasa recta (DVR),  $F_{\text{AVR}}(0)$  and  $C_{\text{AVR}}(0)$  are volume flow and concentration of fluid leaving in the ascending vasa recta (AVR), and  $T_{\text{H}_{20}}$  and  $T_s$  now denote total solute and water absorption from the medullary nephrons. Denoting  $C_{\text{AVR}}(0) - C_{\text{DVR}}(0)$  by  $\Delta C$  and using equation 12, we can rewrite equation 13 as

$$T_{s} = T_{H_{0}0}C_{DVR}(0) + [F_{DVR}(0) + T_{H_{0}0}] \Delta C.$$
 14.

This is the fundamental conservation equation for nephrovascular coupling in the renal medulla. It shows that solute supplied by the nephrons and returned to the systemic circulation by the blood vessels can be split into two fractions. The first,  $T_{\rm H_2O} C_{\rm DVR}(0)/T_s$ , is the solute that carries with it an isotonic complement of water. It is this solute that is used for concentration. The second,

 $[F_{\text{DVR}}(0) + T_{\text{H}_20}]\Delta C/T_s$ , is due to the concentration difference between ascending and descending vascular flows; this solute is unavailable for concentration. Clearly to concentrate urine the kidney must maximize the first fraction and minimize the second wasted fraction, which we will designate as  $T_W/T_s$ . This is accomplished by minimizing  $\Delta C$  by highly efficient vascular exchange. We return to the problem of relating  $T_W$  to vascular permeabilities below. Now, continuing our conservation analysis and introducing the subscripting convention 1 for DHL, 2 for AHL, and 3 for CD, we have the mass balance equations

$$F_{1v}(L) C_1(L) + T_{1s} = F_{1v}(0) C_1(0),$$
 15

$$F_{2v}(L) C_2(L) + T_{2s} = F_{2v}(0) C_2(0), 16.$$

$$F_{3v}(L) C_3(L) + T_{3s} = F_{3v}(0) C_{3v}(0)$$
17.

for solute; and for volume flow we have the equations

$$F_{1v}(L) + T_{1v} = F_{1v}(0), 18.$$

$$F_{2v}(L) + T_{2v} = F_{2v}(0), 19.$$

$$F_{3v}(L) + T_{3v} = F_{3v}(0), 20.$$

where  $F_{1v}(L)$  is volume flow in the DHL at the papillary tip,  $T_{1s}$  is net total outward solute transport in DHL between the corticomedullary junction and papillary tip, and  $T_{1v}$  is net outward water transport in DHL with analogous definitions for the other subscripts.

From isolated tubule data, the AHL is known to be nearly water impermeable (17). From micropuncture experiments, the osmolality in all tip structures is nearly the same in the concentrating kidney (12, 20, 42, 43, 84). In the concentrating kidney, fluid entering the DHL and CD from the cortex is thought to be in osmotic equilibrium with the cortical interstitium. Hence, it is reasonable to assume that  $T_{2v} = 0$ , that  $C_1(L) = C_2(L) = C_3(L) = C_M(L)$  and that  $C_1(0) = C_3(0) = C_{pM}$ , where:  $C_{pM}$  denotes plasma osmolality. With these assumptions we have

$$T_{\rm H_20} = (T_{1v} + T_{3v})$$
 and 21.

$$T_s = (T_{1s} + T_{2s} + T_{3s}).$$

On adding equations 15 and 17 and making some substitutions we obtain

$$[F_{1v}(L) + F_{3v}(L)]C_{M}(L) (1 - \frac{1}{r}) = T_{2s} - T_{W},$$
23.

where r is the concentration ratio  $C_{M}(L)/C_{pM}$ . Equation 23 can be rearranged to give the dimensionless mass balance equation

$$r = \frac{1}{1 - f_T(1 - f_u)(1 - f_w)},$$
 24.

where  $f_T \equiv T_{2s}/[F_{1v}(L) C_M(L)]$  is the fractional solute transport out of AHL,  $f_U \equiv F_{3v}(L)/[F_{1v}(L) + F_{3v}(L)]$  is the fractional urine flow, and  $f_W \equiv T_W/T_{2s}$  is the fractional dissipation of solute by the vascular exchanger. As we have derived this equation, it applies to a single looped nephron. The above derivation is a modification of earlier treatments (64-66) and can be extended to multinephron models (69). The reader should note that the equation is totally independent of transport mechanism and so is valid for concentration by any mixture of solute cycling or water extraction. The most striking feature of the equation is its exhibition of the extent to which a small urine flow or a slight vascular washout decreases the concentration ratio. Thus, if  $f_T = 0.9$  and  $f_W = f_U = 0$ , we calculate r = 10, but if  $f_T = 1 - f_U = 1 - f_W = 0.9$ , then r = 3.7, a drastic reduction in concentrating ability.

# APPROXIMATE ANALYTIC THEORY OF THE MEDULLARY COUNTERFLOW SYSTEM

Flow and concentration in the vasa recta obey the general conservation equations 1 and 2, with transmural solute transport being determined by the sum of a diffusive and a drag turn, i.e. for DVR we have

$$J_s = h_s(C_5 - C_4) + J_v(1 - 0) \frac{C_5 + C_4}{2},$$
 25.

where  $C_5$  is the concentration in DVR,  $C_4$  is the concentration in the surrounding medullary interstitium,  $h_s$  is the salt permeability, and  $\sigma$  is the Staverman reflection coefficient. We will assume that the capillaries are sufficiently permeable so that  $\sigma \simeq 0$ . Under this assumption

$$J_{s} = [h_{s} - J_{\nu}/2] (C_{5} - C_{4}) + J_{\nu}C_{5}. \qquad 26.$$

From equations 1 and 26 we obtain for DVR

$$F_5 \frac{dC_5}{dx} = -[h_s - J_{5v}/2](C_5 - C_4), \qquad 27.$$

with an analogous equation for concentration  $C_6$  in ascending vasa recta, i.e.

$$F_6 \frac{dC_6}{dx} = -[h_s - J_{6v}/2] (C_6 - C_4).$$
28.

From equations 27 and 28 we find

$$C_6 - C_5 = \frac{F_5}{h_s - J_{5\nu}/2} \frac{dC_5}{dx} - \frac{F_6}{h_s - J_{6\nu}/2} \frac{dC_6}{dx} = \Delta C.$$
 29.

We note that if there is no convective flow in the interstitium

$$-F_6 = F_5 + F_3 - F_3(L) + F_1 - F_1(L) = F_5 + T_{H_20}.$$
 30.

Under the assumption that  $C_5 \simeq C_6 \simeq C_4$  and  $dC_5/dx \simeq dC_6/dx \simeq dC_4/dx$  both obtain, and noting that the balance equation 14 holds at every medullary level, from equations 29, 30, and 14 we obtain the equation for the vascular interstitial core:

$$D_4 \frac{dC_4}{dx} + F_4 C_4 = \int_x^L J_{4s} dx.$$
 31.

where  $D_4$  is given by

$$D_4 = [F_5 + T_{\rm H_2O}] \left[ \frac{F_5}{h_s - J_{5\nu}/2} + \frac{F_5 + T_{\rm H_2O}}{h_s - J_{6\nu}/2} \right]$$
 32.

and  $F_4$  is the algebraic sum of flows in AVR and DVR.

If uptake of fluid by the vascular loop is small relative to DVR flow and the normalized solute permeability  $h_s$ , we have the approximate relation  $D_4 \simeq 2[F_{\text{DVR}}]^2/h_s$ . From equation 32, we see  $D_4$  is an effective diffusion coefficient for the core. An alternative derivation of  $D_4$  is to view vascular exchange as a two-dimensional random walk (64).

For DHL and CD we have the conservation equations

$$F_1(x) C_1(x) - F_1(L)C_1(L) = \int_x^L J_{1x} dx, \qquad 33.$$

and

$$F_3(x)C_3(x) = F_3(L)C_3(L) = \int_x^L J_{3s} dx.$$
 34.

Addition of equations 31, 33, and 34 and the assumption that core, DHL, and CD are in osmotic equilibrium, i.e.  $C_4 \simeq C_1 \simeq C_3$ , leads to the equation for the core concentration.

$$-D_4 \frac{dC_4}{dx} + [F_1(L) + F_3(L)] C_4 - [F_1(L) + F_3(L)] C_4(L) = -\int_x^L J_{2s} dx, \quad 35.$$

with the equation for AHL

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$$F_1(L) \left[ C_2(L) - C_2(x) \right] = \int_x^L J_{2s} \, dx. \tag{36}$$

If  $J_{2s}$  is constant, equation 35 is readily integrated and we find that the fractional dissipation is given by (64)

$$f_W = (1 - e^{-KL})/KL,$$
 37

where  $K = [F_{1v}(L) + F_{3v}(L)]/D_4$ . As KL increases from 0 to  $\infty$ ,  $f_W$  decreases from 1 to 0. Concommitantly, the concentration ratio goes from 1 to the limit set by fractional transport and fractional urine flow, which is

$$r = \frac{1}{1 - f_T (1 - f_U)}.$$
 38.

At one extreme with KL = 0 and  $f_W = 1$ , the solute supplied by the diluting segment extracts no water from CD and DHL. From a functional point of view this corresponds to the straight amphibian kidney. At the other extreme, as nephron and vasculature are folded into a loop with tightly coupled ascending and descending flows,  $KL \rightarrow \infty$  and  $f_W \rightarrow 0$ . This corresponds to the intricately structured kidney of the desert rodent. Now the only way solute supplied by the diluting segment can be returned to the systemic circulation is by extracting water from DHL and CD. In this tightly folded structure, from a functional point of view, vasa recta and interstitium form a tube closed at the papillary end and open at the cortical end, which we have called the central core (Figure 2). The upflowing solution in this core equilibrates osmotically with the downflowing solution in DHL and CD, and as  $f_W \rightarrow 0$ , the general equation

$$T_{\rm H_{2}O} = T_{\rm s}(1 - f_{\rm W})/C_{pM}$$
 39.

approaches the limiting equation  $T_{H_2O} = T_s/C_{pM}$ . Thus, the general function of the medullary counterflow system is to insure that each aliquot of solute supplied by the diluting segment is returned to the systemic circulation with its isotonic complement of water.

#### Free Water

This view of the concentrating mechanism can be easily related to the classic clearance concept of negative free water. This is the amount of water that must be added to the final urine to return it to isotonicity, i.e.

$$-T_{\rm H_{o}0}^{\rm C} = U C(L)/C_{\rm p} - U = (r-1)U, \qquad 40.$$

where  $U = F_{CD}(L)$  is the final urine flow. In our model of the concentrating mechanism, if  $f_W = 0$ , then the fluid returned to the systemic circulation by the AVR is iso-osmotic with DVR. In this case the sum of the AHL fluid supplied to the distal nephron and of the final urine must be iso-osmotic, or

$$F_{\text{AHL}}(0) \ C_{\text{AHL}}(0) + F_{\text{CD}}(L) \ C_{\text{CD}}(L) = [F_{\text{AHL}}(0) + F_{\text{CD}}(L)]C_{pM}.$$
41.

Equation 41 can be rearranged to give

$$F_{AHL}(0) [C_{pM} - C_{AHL}(0)] = F_{CD}(L) [C_{CD}(L) - C_{pM}].$$
42

From the equations describing the system it is easy to show (65) that

$$F_{AHL}(0) \left[ C_{pM} - C_{AHL}(0) \right] = f_U T_{2s}.$$
43.

From equations 40, 42, and 43 we obtain

$$f_U T_{2s} / C_{pM} = U(r-1) = -T_{H_20}^C.$$
44.

In a nonideal system  $T_{2s}$  is replaced by  $(1 - f_W) T_{2s}$  to give us

$$f_U(1 - f_W) T_{2s} / C_{pM} = -T^c_{H_2 0}.$$
45.

Thus, we have an equation that precisely relates Smith's negative free water to solute transport out of the AHL system.

# A Note on the S-Shaped Counterflow System

An inevitable consequence of forming the loop of Henle is that a cortical loop is also formed. This cortical loop is as essential to the formation of a concentrated urine as the medullary loop. Overall, the medulla returns an isotonic or slightly hypertonic absorbate to the circulation. The solute free water generated in the AHL system must be removed in the cortex. If it returned to the medulla in the CD system and was removed there, the net effect at most would be an isotonic urine. This water is removed in the cortex by solute supplied by proximal tubule and arterial blood. This water extraction from the distal nephron inevitably dilutes the cortical interstitium to some extent. If this dilution is not to be too severe, cortical blood flow must be large relative to the water absorbed, which is

$$T_{\rm H_2O} = T_{2s} \left[ 1 - (1 - f_W) (1 - f_U) \right] / C_{\rho M}.$$
46.

It will be noted that the water absorbed in the distal nephron is greater than the negative free water by  $f_W T_{2s}/C_{pM}$ . The concentration in the cortical interstitium is given by

$$C_{pM} - C_I \simeq \frac{T_{2s} \left[ f_U + f_W - f_U f_W \right]}{CPF},$$
47.

where CPF is cortical plasma flow.

### COMPUTER SIMULATION

Although the analysis of the medullary counterflow system by conservation principles and the approximal analytic theory of nephrovascular coupling together illuminate many of the functional features of the concentrating mechanism, any detailed correlation of theory and experiment must depend on the numerical solution of the flow equations for the kidney. In the past few years a large number of computer simulations of the medullary counterflow system have been published (1, 11, 19, 49, 53, 54, 72-76).<sup>1</sup>

In virtually all of these simulations, the medulla is viewed as a network of exchanging flow tubes. The differential equations for these tubes are then solved numerically by one or another scheme. Space does not permit a critical discussion of the various numerical techniques that have been used; the interested reader is referred to a recent symposium (14, 24, 32, 33, 41, 50-52, 70, 77).

Approximating the differential equations by a set of finite difference equations and solving these by a modified Newton-Raphson method (74) has proved the most generally satisfactory of the various methods we have tried. We have now used what is basically this solution technique for a hierarchy of models, ranging from a prototype two-tube central core model to a multinephron multisolute model of the whole kidney to give both steady-state and transient solutions. In a general way it can be said that the iterative scheme converges satisfactorily if a solution of the difference equations exists and if the initial estimate is close enough to that solution. From a practical point of view, the principal problem is in solving the system of linear equations (which can be several hundred in number) that arise in the method. Here sparse matrix methods (10, 78, 79) or some partitioning technique (48) is essential. How closely the solutions of the difference equations approximate solutions of the parent differential equations is a more difficult question. This problem has been treated in a general way by Keller for two-point

<sup>&</sup>lt;sup>1</sup> Elsewhere we have given a more complete bibliography of mathematical models of the kidney and its subsystems (71).

boundary value problems (28, 29). His analysis can be shown to carry over to the kidney equations (R. P. Tewarson, J. L. Stephenson, P. Farahzad, and R. Mejia, unpublished results).

Questions of existence and uniqueness are pertinent, because even for simple models solutions either do not exist or are nonunique for certain choices of parameters (J. L. Stephenson and R. B. Kellogg, unpublished results). For some simple models it has been possible to establish conditions for existence and uniqueness (30, 31; J. Garner and R. B. Kellogg, unpublished results).

Other authors have used other numerical techniques to solve the equations for models of the medulla. Foster, Jacquez & Daniels have used quasilinearization to solve the steady-state equations of the central core model (11). Ang, Landahl & Bartoli have used explicit integration schemes to solve the transient equations (1), as have Moore, Marsh & Kalaba (51).

In practice, solutions are built up from known solutions either by following the transient response after variation of a boundary condition or parameter, or by computing a new steady-state solution vector after a small change in a boundary condition or parameter. Both methods were used to calculate the results that follow.

# PERMEABILITY REQUIREMENT FOR CONCENTRATION

In deriving the approximate analytic theory of the concentrating mechanism, a series of limiting assumptions were made in regard to permeabilities of nephron and capillaries. In particular it was assumed that DHL and CD equilibrate osmotically with the surrounding interstitial vascular core. This is clearly essential if the solute supplied by the AHL is to extract water from the CD and DHL. In the absence of such equilibration, the solute would increase the concentration of the core but not of the descending flow. This problem can be examined in the simple prototype model shown in Figure 5, in which vasa recta and interstitium



Figure 5 Prototype two-tube central core model showing water extraction from descending flow generated by net solute supplied to the core. Concentrating ability is limited by the hydraulic permeability of the membrane separating descending flow and core (74).



Figure 6 Concentration profiles in descending flow of prototype model for different hydraulic permeabilities  $h_v$  of DHL (74).

have been merged into a central core and CD and DHL have been merged into a single descending flow. The AHL source was adjusted so that  $f_T(1-f_U) = 0.9$ , which gives a limiting concentration ratio of 10. The effect of varying the hydraulic permeability of the DHL is shown in Figure 6, where concentration profiles in DHL are plotted for different normalized values of the hydraulic permeability. As can be seen there is a critical range of hydraulic permeability around  $h_v = 100$ , below which concentration falls off rapidly and above which the concentration approaches the theoretical limit for ideal osmotic exchange. The easiest way to grasp the physiological significance of  $h_v$  is to note that for  $h_v = 100$  the osmotic driving force for water movement would vary from 13 mOsmol/liter at the corticomedullary junction to 0.38 mOsmol/liter at the papillary tip. Translated into convectional units, for a DHL flow of 6 nl/min at the corticomedullary junction, a DHL diameter of 20  $\mu$ m, and a total medullary depth of 1 cm, the normalized permeability  $h_v = 100$  corresponds to an osmotic coefficient  $L_p \simeq 2 \times 10^{-4}$  ml cm<sup>-2</sup> sec<sup>-1</sup>atm<sup>-1</sup>. The measured value in isolated rabbit tubule is  $1.62 \times 10^{-4}$  ml cm<sup>-2</sup>  $sec^{-1}atm^{-1}(34)$ . This value corresponds to a normalized value of 80 and would lead to a concentration ratio of about 6 in the prototype model.

From the analytic theory of nephrovascular coupling, it is clear that the concentrating ability of the kidney is critically dependent on the exchange efficiency of the vasa recta. As this increases the concentration ratio approaches the limit set by the hydraulic permeability of DHL. This point is illustrated by replacing the core of the prototype model by a vascular exchanger (Figure 7). In Figure 8, concentration profiles of this model are plotted for increasing values of  $h_s$ , with the normalized solute permeability of the membrane separating AVR and DVR. As  $h_s$  increases, *KL* increases and the profiles approach as a limit the profile of the prototype model with  $h_v = 100$ . Very few data are available on the vascular parameters, but from experiments by Marsh & Segel (46) we estimate a *KL* value



Figure 7 Prototype model with core replaced by vascular exchanger (74).



Figure 8 Concentration profiles in prototype vascular exchanger model as a function of the normalized solute permeability  $h_s$  of the vasa recta. Normalized hydraulic permeability  $h_v$  of DHL was 100 in these calculations (74).

in the hamster of about 20. This is of the order of magnitude demanded by theory. The reader should note that from the elementary theory of the concentrating mechanism, the primary limit on the concentrating mechanism is the fractional solute transport out of AHL, and the concentration ratio can never exceed  $1/(1-f_T)$ .

# THE ROLE OF UREA CYCLING IN THE CONCENTRATION OF URINE

It is a well-established experimental observation that protein-depleted mammals have decreased ability to concentrate urine (7); it has also been observed that although large urea loads cause an osmotic diuresis, smaller loads do not (62). As understanding of the medullary counterflow system increased, it was appreciated that urea undergoes a complicated cycle (Figure 9) (81). Approximately one half



Figure 9 Urea cycling in the concentrating kidney. About half the filtered urea is absorbed proximally. Of the fraction that reaches the CD, a small amount escapes in the urine. The rest diffuses out into the medullary interstitium. Some is returned to the systemic circulation. The remainder is recycled via loop of Henle and distal nephron. This recycling can lead to a urea flow in distal nephron that is greater than the filtered load. Thick arrows indicate net flow of urea; thin arrows indicate countercurrent exchange. [Reprinted by permission from Ullrich, K. J., Kramer, K., Boylan, J., 1962, In *Heart, Kidney and Electrolytes*, New York: Grune and Stratton (81).]

of the filtered urea is absorbed in the proximal tubule, and the remainder enters DHL, where like salt it is concentrated by the osmotic removal of water. In the concentrating kidney, it is further concentrated in the distal cortical nephron by the reabsorption of water. In the outer medulla CD urea is concentrated still more. On reaching the papilla CD fluid has a higher urea concentration than the surrounding interstitium and urea diffuses into the interstitial vascular core. Here part of it leaks back into the loop of Henle to be recycled and part of it is returned to the systemic circulation by the vascular counterflow system. The traditional explanation of the urea effect is that the recycled urea is "trapped" by the medullary counterflow system and so augments the concentration (4). This explanation, however, requires modification under detailed analysis. If urea is added to arterial plasma and salt transport remains fixed, even though part of it is recycled, it still acts as an osmotic diuretic; it both decreases fractional transport out of AHL and increases fractional urine flow, and the net effect is a decrease in the concentration ratio [see below, Figure 10 (67)]. Some other explanation must be sought. This explanation emerged from the theoretical analysis of the central core model. This analysis showed that the urea entering the core induces additional salt transport out of AHL given appropriate permeabilities of the various medullary structures (64, 66). Concurrently, it was found from experiments on isolated rabbit tubules that they possessed the required permeabilities (17, 34, 35), and it was independently postulated that in a two-solute system, concentration could occur in the absence of active salt transport out of AHL (36).



Figure 10 The effect of increasing urea load on the concentration ratio for various salt permeabilities  $h_{2s}$  of AHL. For  $h_{2s} = 0$ , there is no induced additional AHL transport and concentration decreases, because of the diuretic effect of urea loading. As  $h_{2s}$  increases, the induced transport becomes the predominant effect (67).

The basic mechanism by which urea cycling induces salt transport out of the ascending limb is easily understood from the analytic theory of the central core model (64, 66). From Equation 31 we have at any medullary level

$$F_{4v} C_{4s} - D_{4s} \frac{dC_{4s}}{dx} = T_{4s}$$
48.

and

where  $F_{4v}$  is volume flow in the core,  $C_{4s}$  is salt concentration,  $C_{4u}$  is urea concentration,  $T_{4s}$  is net salt transport into the core between the papillary tip and the other medullary levels, and  $T_{4u}$  is net urea transport.

If diffusive transport is small relative to convective, valid everywhere except at the very tip for efficient enough vascular exchange, we find from equations 48 and 49

$$C_{4s}/C_{4M} = T_{4s}/(T_{4s} + T_{4u})$$
 50.

and

$$C_{4u}/C_{4M} = T_{4u}/(T_{4u} + T_{4s}), \qquad 51.$$

where  $C_{4M} = C_{4s} + C_{4u}$ . From equation 50 it is clear that as the urea transport into the core increases, the fraction of the total osmolality due to salt decreases.

It is easy to show from the central core equations that at any point along the medullary axis we have (64)

$$C_{4M}(x) - C_{2M}(x) = [C_{4M}(L) - C_{4M}(x)] \frac{f_U}{1 - f_U}, \qquad 52.$$

which yields

$$C_{2s}(x) - C_{4s}(x) = -\left[C_{4M}(L) - C_{4M}(x)\right] \frac{f_U}{1 - f_U} + C_{4M}(x) \frac{T_{4u}}{T_{4u} + T_{4s}} - C_{2u}(x).$$
53.

Equation 53 can be manipulated in various ways, but in the above form it shows the various factors that influence the difference in salt concentration between AHL and core. With no urea in the system, it is clear that salt concentration in AHL is always less than, or at most equal to, core salt concentration. As urea concentration in the system increases there are two opposing effects. The first, urea entry into the core, depresses core salt concentration relative to AHL. The second, which is urea entry into the loop of Henle, either from PT or by diffusion from the core space, increases  $C_{2u}(x)$  and so has the opposing action of depressing AHL salt concentration relative to core salt concentration.

The change in  $C_{2s}(x) - C_{4s}(x)$  affects  $J_{2s}$  by changing diffusive transport, thus

$$J_{2s} = \mathcal{J}_{2s} + h_{2s}(C_{2s} - C_{4s}), \qquad 54.$$

where  $J_{2s}$  is active transport and  $h_{2s}$  is the salt permeability of AHL. Under the assumption that active transport is affected only slightly by urea loading, we have

$$\Delta J_{2s} / \Delta (C_{2s} - C_{4s}) = h_{2s}.$$
55.

Thus, the change in AHL salt transport for a given change in  $C_{2s} - C_{4s}$  is proportional to the salt permeability of AHL.

Given the appropriate transport parameters and urea loading,  $C_{2s} - C_{4s}$  can become positive and net transport out of AHL can take place with no active transport (64, 66). This possibility has been emphasized by Kokko & Rector (36). This is a very attractive idea because it resolves the long-standing problem of demonstrating active transport out of the AHL in the inner medulla (47). It should be noted that the general idea of concentration by solute mixing was suggested many years ago by Kuhn & Ryffel (40).

Whether or not, however, active salt transport occurs in thin AHL is irrelevant to the augmentation of concentration by urea cycling. This augmentation depends first on the change in  $C_{2s} - C_{4s}$  effected by the total urea  $T_{4u}$  delivered to the medullary core. Secondly, it depends on salt permeability  $h_{2s}$  of AHL. In Figure 10 we show the effect of increasing urea concentration in DHL flow for a model of the inner medulla, in which the ratio of cortical to juxtamedullary nephrons is 5 to 1. It was also assumed that enough of the urea was recycled so that the urea entering the distal nephron was twice the filtered load, thus 10 times the filtered load of urea enters the CD. As can be seen, if the salt permeability of the AHL,  $h_{2s}$ , is 0, urea acts simply as an osmotic diuretic and decreases the papillary concentration. As the salt permeability of the AHL is increased, urea cycling generates increased salt transport out of AHL. At first, this only partially mitigates the osmotic divisition but for a sufficiently large  $h_{2s}$  the increased salt transport becomes the dominating effect. In these calculations it was assumed that DHL in the inner medulla is impermeable to urea, so that urea recycling occurs via the short loops. In Figure 11, the effect of increasing the urea permeability of DHL is shown. As can be seen, a small urea leak into DHL rapidly decreases the concentrating effect. This has proved the main obstacle in modeling the inner medulla with a completely passive mechanism. If the urea permeability of DHL is increased enough to give the urea concentration observed by micropuncture. the concentration gradient in the inner medulla is markedly reduced. So far, however, simulations have not taken account of the heterogeneity of the nephron population of the inner medulla. This may facilitate the passive mechanism but any quantitative estimate must await detailed computation. Several recent experimental studies have attempted to assess the exact role of urea in the concentrating mechanism (18, 23, 25, 45, 55). Their results have all been consistent with the idea that urea cycling induces passive salt transport out of the thin AHL, but have not yet defined the relative roles played by passive and active transport in the inner medulla.



Figure 11 The effect of urea leak into DHL. As urea permeability  $h_{1u}$  increases, induced AHL source decreases and the concentrating effect rapidly diminishes (67).

# FREE ENERGY BALANCE IN THE KIDNEY

There are two aspects of renal energetics. The first is the coupling of metabolic energy to transport against an electrochemical gradient. The second is the split of the free energy created by active transport into useful osmotic work and dissipation. Not enough is known about the details of the transport mechanisms to analyze theoretically the coupling of chemical reactions to active transport. The second problem has been analyzed in considerable detail (68, 82).

This analysis for an arbitrary steady-state open system with no chemical sources at constant temperature and pressure leads to the general balance equation for the counterflow system for the renal medulla

$$RT\Sigma_{k} \{F_{Uk} \ln(C_{Uk}/C_{Ok}) - \Sigma_{i} [F_{ik} \ln(C_{ik}/C_{Ok})]_{x=0} \}$$
  
=  $RT\Sigma_{k} \int_{o}^{1} \sum_{\substack{i,p \\ i > p'}} - [h_{ip,k}(C_{ik} - C_{pk}) + \mathcal{J}_{ip,k}] \ln(C_{ik}/C_{pk}) dx$   
 $- \int_{0}^{1} \sum_{\substack{i,p \\ i > p}} RTh_{ip,v}(C_{iM} - C_{pM})^{2} dx,$  56.

where  $F_{ik}$  is the axial flow and  $C_{ik}$  is the concentration of the kth solute in the *i*th tube;  $h_{ip,k}$  is the permeability of the membrane separating the *i*th from the *p*th tube for the kth solute;  $h_{ip,v}$  is its hydraulic permeability; R is the universal gas constant; T is the absolute temperature;  $\mathcal{J}_{ip,k}$  is active transport of the kth solute from the *i*th to the *p*th tube;  $C_{Ok}$  is a reference concentration for the kth solute (usually one of the entering concentrations);  $F_{Uk} = (\sum_i F_{ik})_{x=1}$  is the CD

outflow of the kth solute;  $C_{iM}$  is total solute concentration in the *i*th tube; and  $C_{Uk}$  is the concentration of the kth solute in the CD outflow.

The left side of equation 56 is the rate at which free energy outflow from the medulla exceeds free energy inflow. The right side is the rate at which free energy is being created or destroyed by transport of solutes and water across the membranes separating the tubes. With the exception of the term  $\mathcal{J}_{ip,k} \ln (c_{ik}/c_{pk})$ , all terms on the right side of equation 76 are negative and represent power dissipation in the membranes. Thus,  $-(RT)^2 \int_0^1 h_{ip,v} (C_{iM} - C_{pM})^2 dx$  is the rate of energy dissipation caused by the osmotic flow of water. This integral can also be written  $-(\underline{RT})^2 \,_0 \int^1 (J_{ip,v})^2 dx/h_{ip,v}$  and hence for a given water extraction from DHL and CD is inversely proportional to the hydraulic permeability. Relative power use in the medulla for a single nephron coupled to a single vascular loop is shown in Table 1. This calculation shows that of the power supplied by active transport, about 40% is dissipated by inefficient vascular exchange and 50% by the transmural transport of water and solutes, which leaves only about 10% for solute concentration in the final urine. This calculation ignores viscous dissipation, which Weinstein (82) has shown contributes terms of the form  $-\int_0^1 R_{iF}(F_{iv})^2 dx$ . Although this calculation embodies some rather arbitrary parameter choices, the main resultthat only a small fraction of the free energy supplied by active salt transport ends up as useful osmotic work-seems likely to stand.

Supplied         0.201           AHL <sup>b</sup> 0.799           Total         1.000           Used         0.376           Solute loss vasa recta         0.376           Membrane dissipation         0.096           AHL salt <sup>e</sup> 0.007           AVR salt         0.159           AVR urea         0.024           DHL water         0.207           CD water         0.004           Subtotal         0.497           Solute concentration in urine         Salt <sup>d</sup> Urea         0.119           Total <sup>e</sup> 0.992	Power	Computation
DN         0.201           AHL <sup>b</sup> 0.799           Total         1.000           Used         0.376           Solute loss vasa recta         0.376           Membrane dissipation         0.096           AHL salt <sup>e</sup> 0.007           AVR salt         0.159           AVR urea         0.024           DHL water         0.207           CD water         0.004           Subtotal         0.497           Solute concentration in urine         Salt <sup>d</sup> Urea         0.119           Total <sup>e</sup> 0.992	Supplied	
AHL <sup>b</sup> 0.799         Total       1.000         Used       0.376         Solute loss vasa recta       0.376         Membrane dissipation       0.096         AHL salt <sup>e</sup> 0.007         AVR salt       0.159         AVR urea       0.024         DHL water       0.207         CD water       0.004         Subtotal       0.497         Solute concentration in urine       Salt <sup>d</sup> Trea       0.119         Total <sup>e</sup> 0.992	DN	0.201
Total         1.000           Used         0.376           Solute loss vasa recta         0.376           Membrane dissipation         0.096           CD urea         0.096           AHL salt <sup>e</sup> 0.007           AVR salt         0.159           AVR urea         0.024           DHL water         0.207           CD water         0.004           Subtotal         0.497           Solute concentration in urine         Salt <sup>d</sup> Urea         0.119           Total <sup>e</sup> 0.992	AHL <sup>b</sup>	0.799
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Total <sup>e</sup> 0.992	Urea	0.119
	Total <sup>e</sup>	0.992

<b>1 able 1</b> Relative power use in the relial filed
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<sup>a</sup> Computations are for  $h_{3u} = 0.02$  and  $h_{2s} = 10$  for a single nephron model.

<sup>b</sup> Active transport integral for thick AHL. <sup>c</sup> Passive diffusion integral for thin AHL.

<sup>d</sup> Because of active salt transport out of AHL and DN a negligible amount is excreted in final urine for this case.

• The difference 0.008 between supply and use represents the cumulative error of the various integrations.

# SUMMARY

In this review the renal counterflow system has been analyzed as a coupled nephrovascular unit. The basic functional feature of this S-shaped system is that it permits solute supplied by the diluting segment (AHL) to extract water from the CD system. Secondarily, it also permits this solute to extract water from DHL or to be recycled via DHL.

The water extracted for a given quantity of solute supplied depends upon the exchange efficiency of the vascular counterflow system. The basic equation that relates water extraction to solute supplied by the diluting segment is

$$-T_{\rm H_{2}0}^c = T_{2s}(1-f_{\rm W}) f_{\rm U}/C_{\rm PM},$$

where  $-T_{\rm H_20}^c$  is the classic negative free water, i.e. the quantity of water that would have to be added to the final urine to return it to isotonicity with plasma,  $T_{2s}$  is net solute supplied by ascending Henle's limb,  $1 - f_W$  is the efficiency of the exchanger,  $f_U$  is the ratio of final urine flow to the sum of CD and loop of Henle flow at the papilla, and  $C_{pM}$  is plasma osmolality. The ratio of the osmolality of final urine to plasma is given by

$$r = 1/[1 - f_T(1 - f_U)(1 - f_W)],$$

where  $f_T$  is fractional transport out of AHL. An approximate analytic theory of the counterflow system gives  $f_W = [1 - \exp(-KL)]/(KL)$ , where the dimensionless parameter KL approximately equals  $h_s L[F_{CD}(L) + F_{DHL}(L)]/[F_{DVR}]^2$ . Thus, the efficiency of the vascular exchanger tends toward unity as the product of the vascular permeabilities, length of the medulla, and sum of the volume flow in CD and DHL at the papilla increase and tends toward zero as the square of the vasa recta flow increases.

Detailed numerical calculations on a hierarchy of models of the whole kidney and medulla have supported the qualitative conclusions drawn from the analytic theory.

Both the analytic theory and the detailed calculations give a new explanation of the way in which urea augments concentration. The classic view has been that urea diffusing in from CD is "trapped" by the counterflow system and simply sums with salt to increase concentration. However model calculations show that this urea cycling diminishes but does not prevent a diuretic effect. They also show that as urea from CD and water from CD and DHL enter the vascular interstitial core they dilute the salt, which depresses core salt concentration relative to the loop of Henle salt concentration and so generates a salt source out of AHL that is proportional to the product of the increment in the concentration difference by the passive salt permeability of AHL. This induced source adds to any active transport out of AHL and causes an increase in the medullary concentration gradient. Model simulations show that with suitable parameters the inner medulla can concentrate with no active transport. Whether or not this happens in reality is still experimentally moot.

A detailed thermodynamic analysis has permitted calculations of energy balance

in various models. In general, only a small fraction of the free energy generated by active salt transport in AHL and distal nephron goes into useful osmotic work; the rest is lost to the systemic circulation by inefficient vascular exchange or is dissipated by viscous flow and by passive transmembrane transport of salt, water, and urea.

### Future Directions

During the past few years enormous progress has been made in both the theoretical understanding and computer simulation of renal function. With an experimentally determined or assumed set of transport parameters, it is now possible to simulate renal function with a model that includes salt, urea, and water movement, and hydraulic and oncotic pressure, and that takes account of the heterogeneity of the nephron population. This seems adequate for at least a preliminary correlation of microscopic and clearance data. Many of the details of this comparison remain to be worked out, but preliminary calculations have shown that the parameters found in isolated tubule studies are of the correct order of magnitude for reasonable overall function.

In the next few years one can expect that the models will be extended in complexity to take account of some of the finer details of renal architecture that have been worked out by Kriz, Beeuwkes, and others (2, 9, 26, 37). Until this fine structure is modeled in some detail we will not know how adequate our approximating models are.

During the past 25 years the classic approach to renal physiology via clearance concepts has gradually shifted to a microscopic approach with emphasis on the underlying membrane physiology and biochemistry. In the absence of adequate models, this microscopic data cannot be synthesized into an understanding of whole organ function. Conversely, the inversion of measurements on whole organ function to give estimates of transport parameters is an even more difficult problem. It requires first an adequate model and second a very sophisticated technique of systems identification. It is our prediction that modeling is going to create a new interest in the whole organ physiology of the kidney that will complement the microscopic and submicroscopic dissection of renal physiology.

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