CONCENTRATING ENGINES AND THE KIDNEY

III. CANONICAL MASS BALANCE EQUATION FOR MULTINEPHRON MODELS OF THE RENAL MEDULLA

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ABSTRACT The canonical mass balance relation derived for the central core model of the renal medulla is extended to medullary models in which an arbitrary assemblage of renal tubules and vascular capillaries exchange with each other both directly and via the medullary interstitium and in which not all of the vascular loops or loops of Henle extend to the papilla. It is shown that if descending limbs of Henle and descending vasa recta enter the medulla at approximately plasma osmolality, the concentration ratio is given by: $r = 1/[1 - f_T(1 - f_U)(1 - f_W)]$, where f_T is fractional solute transport out of ascending Henle's limb, f_U is fractional urine flow, and f_W is fractional dissipation; f_W is a measure of the solute returned to the systemic circulation without its isotonic complement of water. A modified equation that applies to the diluting as well as the concentrating kidney is also derived. By allowing concentrations in interstitium and vascular capillaries to become identical at a given medullary level, conservation relations are derived for a multinephron central core model of the renal medulla.

INTRODUCTION

In earlier work (Stephenson, 1972; Stephenson, 1973*a*; and Stephenson et al., 1974) it has been shown that the mass balance equation for the central core model and certain simplified models including the vasa recta can be cast into the canonical form

$$r = 1/[1 - f_T(1 - f_U)(1 - f_W)], \tag{1}$$

where r is the ratio of total osmolality at the papilla (assumed approximately the same in all structures) to plasma osmolality, f_T is fractional solute transport out of ascending Henle's limb, and f_U is the fractional urine flow, and f_W, the fractional dissipation in the vascular exchanger, is a measure of the solute that is returned to the systemic circulation by the ascending vasa recta unaccompanied by its isotonic equivalent of water. This normal form of the mass balance equation has proved a useful supplement to intuition in understanding the qualitative behavior of the medullary counterflow system and a useful check on detailed calculation on both models

of the medullary counterflow system (Stephenson et al., 1974) and models of the whole kidney (Stephenson et al., 1976).

In this paper we show that with suitable modifications the equation applies to models of nearly arbitrary complexity. In particular, it applies to models in which an arbitrary assemblage of renal tubules and vascular capillaries exchange with each other both directly and via the medullary interstitium and in which not all of the vascular loops or loops of Henle extend to the papilla. We also derive a modified equation that applies to the diluting as well as the concentrating kidney. In deriving these equations the primary restriction is that the total osmolality of fluid entering the descending limbs of Henle and the descending vasa recta closely approximates the total osmolality of plasma. Formally the derivation is analogous to that for the central core model, except that summations are taken over distributions of flow tubes.

CONSERVATION EQUATIONS

In a system of parallel exchanging flow tubes the general steady-state conservation equation for the kth solute in the ith tube is

$$dF_{ik}/dx = -J_{ik}, \tag{2}$$

where F_{ik} is the total axial flow of the solute, J_{ik} is the transmural flux per unit length, and x is normalized length in the direction parallel to the direction of flow, $0 \leq x \leq 1$. The equation for volume flux is

$$dF_{iv}/dx = -J_{iv}. \tag{3}$$

Transport along the axis of flow is

$$F_{ik} = F_{iv}c_{ik} - D_{ik}A_i dc_{ik}/dx \tag{4}$$

where c_{ik} is the concentration of the kth solute in the ith tube, D_{ik} is its diffusion coefficient, and A_i is the cross-sectional area of the tube. We have the additional relations

$$J_{ik} = \sum_j J_{ij,k} \tag{5}$$

and

$$J_{iv} = \sum_j J_{ij,v}, \tag{6}$$

where $J_{ij,k}$ and $J_{ij,v}$ are, respectively, flux of the kth solute and volume flux from the ith to the jth tube. We have by definition

$$J_{ij,k} = -J_{ji,k}, \tag{7}$$

and

$$J_{ij,v} = -J_{ji,v}. \tag{8}$$

From Eq. 5 through 8 it follows by pairwise summation that

$$\sum_i J_{ik} = \sum_i \sum_j J_{ij,k} = 0 \tag{9}$$

and

$$\sum_i J_{iv} = \sum_i \sum_j J_{ij,v} = 0 \tag{10}$$

From Eq. 2, 3, 9, and 10 we have the relations

$$\sum_i F_{ik}(x) = \sum_i F_{ik}(0) = \sum_i F_{ik}(1), \tag{11}$$

and

$$\sum_i F_{iv}(x) = \sum_i F_{iv}(0) = \sum_i F_{iv}(1). \tag{12}$$

It also follows that

$$\sum_k \sum_i F_{ik}(x) = \sum_i \sum_k F_{ik}(x)$$

$$\equiv \sum_i F_{iM}(x) = \sum_i F_{iM}(0) = \sum_i F_{iM}(1). \tag{13}$$

If $D_{ik} \to 0$

$$\sum_i F_{iv}(x)c_{ik}(x) = \sum_i F_{iv}(0)c_{ik}(0)$$

$$= \sum_i F_{iv}(1)c_{ik}(1), \tag{14}$$

and

$$\sum_i F_{iv}(x)c_{iM}(x) = \sum_i F_{iv}(0)c_{iM}(0)$$

$$= \sum_i F_{iv}(1)c_{iM}(1), \tag{15}$$

where by definition total osmolality

$$c_{iM} = \sum_k c_{ik} \tag{16}$$

and total axial osmolal flow

$$F_{iM} = \sum_k F_{ik}. \tag{17}$$

All of the above relations have been derived previously, but only for a system of flow tubes in which all tubes traverse the entire depth of the medulla. These equations

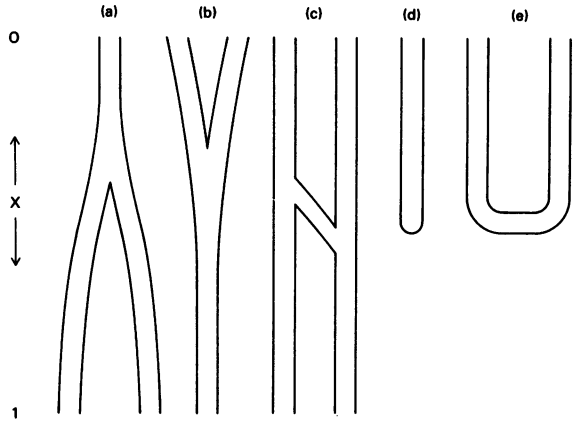

FIGURE 1 Examples of partial traversal of the medulla in a system of flow tubes.

apply equally well to a system of parallel flow tubes (see Fig. 1) that branch, merge, anastomose, form hairpin loops, and arise from blind ends in an arbitrary manner. Thus, Eqs. 7 and 8 apply not only to transmural exchange but for tubes that exchange by anastomosis. Even though all tubes do not traverse the entire medulla we can sum over the same set of indices by replacing the actual system of tubes with an equivalent virtual system in which all tubes traverse the entire medulla, but with $F_{ik} = 0$ and $F_{iv} = 0$ in the virtual extensions. The principle is illustrated in Fig. 2. The hairpin loop of Fig. 2 *a* is replaced by the virtual system of Fig. 2 *b* in which all flows and fluxes in the dotted portions are zero. If this is done for all tubes that merge, branch, reflect, or arise or terminate in blind ends, each tube in the equivalent virtual system will extend from $x = 0$ to $x = 1$. Then in the virtual system Eq. 2 can be integrated from 0 to 1 for each tube to give

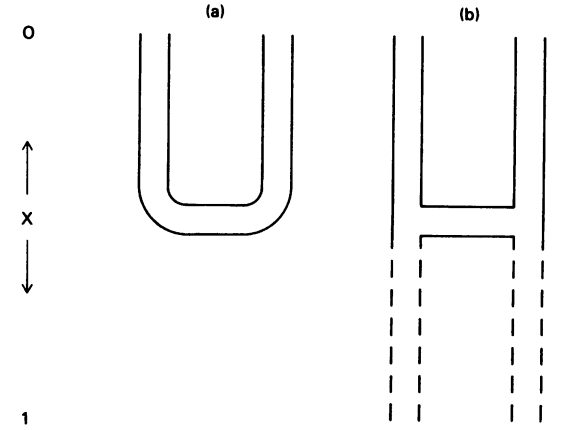

FIGURE 2 (*a*) A loop that does not traverse the entire medulla. (*b*) Replacement by a virtual system of two parallel tubes that do traverse the medulla.

$$F_{ik}(1) - F_{ik}(0) = -\int_0^1 J_{ik}(x)\,dx \equiv -T_{ik}, \tag{18}$$

where T_{ik} is the total transport of the kth solute from the ith tube. We also have from Eq. 2

$$\sum_i (dF_{ik}/dx) = \sum_i - J_{ik} = 0, \tag{19}$$

where for each x the summation extends over all tubes. From Eqs. 18 and 19 and similar equations for F_{iv}, Eqs. 11–17 follow for the virtual system of tubes, whose behavior is identical with the actual system. We also note that we have the relations

$$\sum_i T_{ik} = 0, \tag{20}$$

$$\sum_i T_{iM} = 0, \tag{21}$$

$$\sum_i T_{iv} = 0. \tag{22}$$

It is also clear that the above derivation is equivalent to defining a set of tube indices for the system such that $i \in S$ if tube i traverses *any level* of the medulla. At every medullary level x we then sum over the entire indexing set with the convention that if tube i does not traverse that level then $F_{ik}(x) = F_{iv}(x) = J_{iv}(x) = J_{ik}(x) = 0$.

CANONICAL MASS BALANCE EQUATION

To derive the normalized mass balance equation for our system of flow tubes we partition the set of indices S into the disjoint sets S_1, S_2, S_3, S_4, S_5, S_6, where S_1 is the set of indices for the descending limbs of Henle (DHL), S_2 is the set for ascending limbs of Henle (AHL), S_3 is the set for collecting ducts (CD), S_4 is the set for the interstitium (which we consider partitioned into a set of parallel flow tubes closed at the papillary end), S_5 is the set for descending vasa recta (DVR), and S_6 is the set for ascending vasa recta (AVR). From Eq. 13 and the general properties of summation over a union of disjoint sets we obtain

$$\begin{aligned}\sum_{i\in S} F_{iM}(0) &= \sum_{i\in S_1} F_{iM}(0) + \sum_{i\in S_2} F_{iM}(0) \\ &\quad + \sum_{i\in S_3} F_{iM}(0) + \sum_{i\in S_4} F_{iM}(0) + \sum_{i\in S_5} F_{iM}(0) \\ &\quad + \sum_{i\in S_6} F_{iM}(0) = \sum_{i\in S} F_{iM}(1) \\ &= \sum_{i\in S_1} F_{iM}(1) + \sum_{i\in S_2} F_{iM}(1) + \sum_{i\in S_3} F_{iM}(1) \\ &\quad + \sum_{i\in S_4} F_{iM}(1) + \sum_{i\in S_5} F_{iM}(1) + \sum_{i\in S_6} F_{iM}(1)\end{aligned} \tag{23}$$

If we introduce the summation convention

$$\sum_{i \in S_j} F_{iM}(x) = F_{jM}(x), \tag{24}$$

i.e. $\sum_{i \in S_1} F_{iM}(0) = F_{1M}(0)$, and note the boundary conditions

$$F_{iM}(1) = 0, i \in S_4, \tag{25}$$

and

$$F_{5M}(1) + F_{6M}(1) = 0; \tag{26}$$

we can rewrite Eq. 23

$$F_{1M}(1) - F_{1M}(0) + F_{2M}(1) - F_{2M}(0) + F_{3M}(1) - F_{3M}(0) = F_{4M}(0) + F_{5M}(0) + F_{6M}(0). \tag{27}$$

Similarly we obtain for the volume flow

$$F_{1v}(1) - F_{1v}(0) + F_{2v}(1) - F_{2v}(0) + F_{3v}(1) - F_{3v}(0) = F_{4v}(0) + F_{5v}(0) + F_{6v}(0), \tag{28}$$

and for each individual solute

$$F_{1k}(1) - F_{1k}(0) + F_{2k}(1) - F_{2k}(0) + F_{3k}(1) - F_{3k}(0) = F_{4k}(0) + F_{5k}(0) + F_{6k}(0). \tag{29}$$

It should be noted that in the derivation of Eqs. 27–29 we have introduced no restrictive assumptions relative to diffusive transport. In order to cast Eqs. 27 and 28 into canonical form we note

$$F_{1M}(1) - F_{1M}(0) = \sum_{i \in S_1} \sum_k \{[F_{iv}(x) c_{ik}(x) - D_{ik} \, \mathrm{d}c_{ik}/\mathrm{d}x]_{x=1} - [F_{iv}(x) c_{ik}(x) - D_{ik} \, \mathrm{d}c_{ik}/\mathrm{d}x]_{x=0}\} \tag{30}$$

or

$$F_{1M}(1) - F_{1M}(0) = F_{1v}(1)\overline{c_{1M}(1)} - F_{1v}(0)\overline{c_{1M}(0)} + \Delta_{1D}, \tag{31}$$

where

$$\overline{c_{1M}} = \sum_{i \in S_1} \sum_k F_{iv} c_{ik} \Big/ \sum_{i \in S_1} F_{iv} \tag{32 A}$$

is by definition the mean osmolality of the fluid in the DHL system at x, and where

$$\Delta_{1D} = + \sum_{i \in S_1} D_{ik} \{[\mathrm{d}c_{ik}/\mathrm{d}x]_{x=0} - [\mathrm{d}c_{ik}/\mathrm{d}x]_{x=1}\} \tag{32 B}$$

is the net contribution of the diffusional terms. We have similar equations for S_2, S_3, S_4, S_5, and S_6. We will however, assume that

$$c_{iM}(0) = c_{pM}, i \in S_1 \cup S_5, \tag{33}$$

where c_{pM} is plasma osmolality. We then have

$$\overline{c_{1M}(0)} = \overline{c_{5M}(0)} = c_{pM}. \tag{34}$$

The osmolality of interstitial and ascending vasa recta fluid will differ from plasma osmolality by a quantity that depends on the efficiency of the vascular exchanger, and CD fluid may differ depending on the water and solute reabsorption in the distal nephron. Accordingly, we write

$$\overline{c_{3M}(0)} = c_{pM} + \Delta c_{3M}, \tag{35}$$

$$\overline{c_{4M}(0)} = c_{pM} + \Delta c_{4M}, \tag{36}$$

$$\overline{c_{6M}(0)} = c_{pM} + \Delta c_{6M}. \tag{37}$$

By combining Eq. 31 and similar equations for DVR, AVR, CD, and interstitium and Eqs. 34–37 with Eq. 27, we can write

$$\begin{aligned} F_{1v}(1)\overline{c_{1M}(1)} - F_{1v}(0)\,c_{pM} + F_{3v}(1)\,\overline{c_{3M}(1)} - F_{3v}(0)\,(c_{pM} + \Delta c_{3M}) \\ = T_{2M} + [F_{4v}(0) + F_{5v}(0) + F_{6v}(0)]\,c_{pM} \\ + F_{4v}(0)\,\Delta c_{4M} + F_{6v}(0)\,\Delta c_{6M} - \sum_{j\neq 2} \Delta_{jD}. \end{aligned} \tag{38}$$

Utilizing Eq. 28 we can rewrite Eq. 38

$$\begin{aligned} F_{1v}(1)[\overline{c_{1M}(1)} - c_{pM}] + F_{3v}(1)[\overline{c_{3M}(1)} - c_{pM}] \\ = T_{2M} - T_{2v}c_{pM} + F_{3v}(0)\,\Delta c_{3M} - W \end{aligned} \tag{39}$$

where by definition

$$W \equiv \sum_{j\neq 2} \Delta_{jD} - [F_{4v}(0)\,\Delta c_{4M} + F_{6v}(0)\,\Delta c_{6M}] \tag{40}$$

If $\Delta_{1D} = \Delta_{3D} = 0$, we also have from Eq. 27

$$W = (T_{1M} + T_{2M} + T_{3M}) - (T_{1v} + T_{2v} + T_{3v})c_{pM}. \tag{41}$$

Thus if axial diffusive transport in DHL and CD is negligible, W is the solute in the total medullary reabsorbate that is unaccompanied by its isotonic equivalent of water.

Eq. 39, which is subject only to the boundary conditions in interstitium, vasa recta, and the DHL system, can be rearranged in various ways subject to additional restrictive assumptions. In a concentrating kidney in which $\overline{c_{1M}(1)} \cong \overline{c_{3M}(1)}$, i.e. in which final urine is approximately the same total osmolality as DHL fluid at the papilla, we have from Eq. 39,

$$\begin{aligned} [F_{1v}(1)\,\overline{c_{1M}(1)} + F_{3v}(1)\,\overline{c_{3M}(1)}]\left(1 - \frac{1}{r}\right) \\ = T_{2M} - T_{2v}c_{pM} + F_{3v}(0)\,\Delta c_{3M} - W, \end{aligned} \tag{42}$$

where the *concentration ratio*

$$r \equiv \overline{c_{1M}(1)}/c_{pM} = \overline{c_{3M}(1)}/c_{pM}. \tag{43}$$

Eq. 42 can be rearranged to give the canonical form of the mass balance equation

$$r = 1/[1 - f_T(1 - f_U)(1 - f_W)], \tag{44}$$

where by definition

$$f_T \equiv [T_{2M} - T_{2v}c_{pM} + F_{3v}(0)\,\Delta c_{3M}]/[F_{1v}(1)\,\overline{c_{1M}(1)}], \tag{45}$$

$$f_U \equiv F_{3v}(1)/[F_{1v}(1) + F_{3v}(1)], \tag{46}$$

and

$$f_W \equiv W/[T_{2M} - T_{2v}\,c_{pM} + F_{3v}(0)\,\Delta c_{3M}]. \tag{47}$$

Eqs. 44–47 are formally identical with those derived previously (Stephenson, 1972) for the central core model. The difference is that the AHL solute source T_{2M} in the simple central core models is replaced by the virtual source for the AHL system

$$T^1_{2M} = T_{2M} - T_{2v}\,c_{pM} + F_{3v}(0)\,\Delta c_{3M}. \tag{48}$$

In Eq. 48, $F_{3v}(0)\,\Delta c_{3M}$ measures the effect of nonisotonicity of fluid entering the CD system from the distal nephrons. If this fluid is hypotonic (i.e. Δc_{3M} is negative) then the effective AHL source is decreased. Likewise, $-T_{2v}c_{pM}$ measures the effects of uptake or loss of *solute free* water from the AHL system. Since T_{2v} is the net loss, uptake of water by the AHL system is equivalent to pumping out a total quantity of solute $-T_{2v}c_{pM}$. If $T_{2v} = 0$ and $\Delta c_{3M} = 0$, then T^1_{2M} reduces to T_{2M} and the above equation becomes identical with that derived earlier.

To some extent the way in which Eq. 42 is normalized is arbitrary. Thus we could define $W' \equiv W + T_{2v}\,c_{pM} - F_{3v}(0)\,\Delta c_{3M}$, with corresponding definitions $f'_T \equiv T_{2M}/[F_{1v}(1)\overline{c_{1M}(1)}]$, and $f'_W \equiv W'/T_{2M}$. This alternative formulation has the advantage of retaining the natural definition of fractional transport out of AHL. It has the disadvantage of lumping the various dissipative processes. Regardless of the formulation the reader should note that the concentrating effect of net solute transport out of AHL is dissipated by four processes: (1) axial diffusion, given by $\sum_{j\neq 2}\Delta_{jD}/T_{2M}$; (2) inefficient osmotic equilibration between ascending and descending flows, measured by $-[F_{4v}(0)\,\Delta c_{4M} + F_{6v}(0)\,\Delta c_{6M}]/T_{2M}$; (3) water reabsorption from AHL, measured by $T_{2v}c_{pM}/T_{2M}$; and (4) hypotonicity of CD inflow, measured by $-F_{3v}(0)\,\Delta c_{3M}/T_{2M}$.

If $\overline{c_{3M}(0)}$ differs from c_{pM} and $\overline{c_{3M}(1)}$ differs from $\overline{c_{1M}(1)}$, as will be the case in the diuretic kidney, we can write Eq. 39 in the form,

$$F_{1v}(1)\,\overline{c_{1M}(1)}\left(1 - \frac{1}{r_1}\right) = T_{2M} + T_{3M} - (T_{2v} + T_{3v})\,c_{pM} - W, \tag{49}$$

where

$$r_1 = \overline{c_{1M}(1)}/c_{pM}. \tag{50}$$

Eq. 49 can be cast into the canonical form

$$r_1 = 1/[1 - f_T^1(1 - f_W^1)], \tag{51}$$

where

$$f_T^1 = T^1/[F_{1v}(1)\,\overline{c_{1M}(1)}], \tag{52}$$

$$f_W^1 = W/T^1, \tag{53}$$

and

$$T^1 = T_{2M} - T_{2v}\,c_{pM} + T_{3M} - T_{3v}\,c_{pM}. \tag{54}$$

Eqs. 49–54 are more general than Eqs. 42–47 in that they give concentration in the DHL system in any physiological state of the kidney. These equations show clearly the effect of solute and water transport out of the CD system. In the concentrating kidney $T_{3M} - T_{3v}\,c_{pM} < 0$ and decreases the effective AHL source $T_{2M} - T_{2v}\,c_{pM}$. In the diluting kidney it is possible that $T_{3M} - T_{3v}\,c_{pM} > 0$. It has also been speculated that in the diluting kidney there is relatively more water uptake from CD than in the concentrating kidney, which implies $T_{3M} - T_{3v}\,c_{pM}$ is even more negative than in the concentrating kidney. At present the question of the behavior of $T_{3M} - T_{3v}\,c_{pM}$ in the shift from concentration to diuresis is simply unresolved.

MULTINEPHRON CENTRAL CORE MODEL

The central core model (Stephenson, 1972) was obtained by assuming that the medullary capillaries are so permeable to salt and other small solutes that the vasa recta system and the surrounding interstitium can be merged into a single fluid filled space closed at the papillary end and open at the cortico-medullary junction, where it is supposed to discharge into the systemic circulation. In terms of our present formulation this concept corresponds to the statement that there is a concentration c_{ck} such that

$$c_{ik}(x) = c_{ck}(x), i \in S_c = S_4 \cup S_5 \cup S_6, \tag{55}$$

where S_c is the index set for the core.[1] Eq. 55 permits us to define a core concentration c_{ck}. We then have

$$F_{ik}(x) = F_{iv}(x)\,c_{ck}(x) - D_{ik}A_i\,\mathrm{d}c_{ck}/\mathrm{d}x, i \in S_c. \tag{56}$$

If we sum Eq. 56 over the structures making up the core we obtain

$$F_{ck}(x) = F_{cv}(x)\,c_{ck}(x) - D_kA_c\,\mathrm{d}c_{ck}/\mathrm{d}x, \tag{57}$$

where

[1]The assumption that $c_{ik} \to c_{ck}$, $i \in S_c$, as solute permeabilities become large is equivalent to assuming that transmural fluxes remain bounded.

$$F_{ck}(x) = \sum_{i \in S_c} F_{ik}(x), \tag{58}$$

$$F_{cv}(x) = \sum_{i \in S_c} F_{iv}(x), \tag{59}$$

$$D_k A_c = \sum_{i \in S_c} D_{ik} A_i. \tag{60}$$

These equations can be converted to a more useful form by observing that if instead of integrating the fundamental conservation Eq. 19 over the entire medulla, we integrate from x to 1, we obtain

$$F_{1k}(1) - F_{1k}(x) + F_{2k}(1) - F_{2k}(x) + F_{3k}(1) - F_{3k}(x) = F_{4k}(x) + F_{5k}(x) + F_{6k}(x) \tag{61}$$

with similar equations for total osmolality and volume flow. By combining these equations with Eqs. 58 and 59 we obtain

$$F_{ck}(x) = -[T_{1k}(x) + T_{2k}(x) + T_{3k}(x)] \tag{62}$$

$$F_{cv}(x) = -[T_{1v}(x) + T_{2v}(x) + T_{3v}(x)]. \tag{63}$$

where

$$T_{1k}(x) \equiv \sum_{i \in S_1} \int_x^1 J_{ik}(x)\, dx, \tag{64}$$

with similar defining equations for $T_{2k}(x)$, $T_{3k}(x)$, $T_{1v}(x)$, $T_{2v}(x)$, and $T_{3v}(x)$. Subject to topological restraints, all of the flow tubes belonging to the DHL, AHL, and CD systems may exchange with both the core and each other. The equations for these tubes plus the above equations for the core give a system of differential integral equations. If phenomenological equations are introduced for transmural transport, this system can hopefully be solved by an extension of the methods we have used for simpler models, but the essential point is that the behavior of the model is a *limiting case* in which the behavior is determined by the transport properties of the *nephrons*.

If diffusional transport is negligible then Eq. 57 becomes

$$F_{ck} = F_{cv} c_{ck}, \tag{65}$$

and from Eqs. 62 and 63

$$c_{ck}(x) = [T_{1k}(x) + T_{2k}(x) + T_{3k}(x)]/[T_{1v}(x) + T_{2v}(x) + T_{3v}(x)]. \tag{66}$$

By definition the right-hand side of Eq. 66 is the average concentration of the kth solute in the reabsorbate from the nephrons of the medulla between x and 1. As $x \to 1$, we have

$$c_{ck}(1) = [J_{1k}(1) + J_{2k}(1) + J_{3k}(1)]/[J_{1v}(1) + J_{2v}(1) + J_{3v}(1)]. \tag{67}$$

We also have

$$c_{cM}(x) = [T_{1M}(x) + T_{2M}(x) + T_{3M}(x)]/[T_{1v}(x) + T_{2v}(x) + T_{3v}(x)] \quad (68)$$

and

$$c_{ck}(x)/c_{cM}(x) = [T_{1k}(x) + T_{2k}(x) + T_{3k}(x)]/[T_{1M}(x) + T_{2M}(x) + T_{3M}(x)]. \quad (69)$$

The ideal central core model was obtained by introducing the additional assumption that the water permeabilities of the DHL and CD systems are so large that

$$c_{1M}(x) = c_{4M}(x) = c_{3M}(x), \quad (70)$$

where 4 is the index of the core. In multinephron models this corresponds to the assumption that

$$c_{iM}(x) = c_{cM}(x), i \in S_1 \cup S_3 \cup S_c. \quad (71)$$

Thus, every flow tube except those belonging to the AHL system is osmotically equilibrated at a given medullary level.

Eq. 71 implies that

$$c_{cM}(0) = c_{1M}(0) = c_{3M}(0) = c_{pM}. \quad (72)$$

In turn, Eq. 72 implies by Eq. 40 that $W = 0$; in turn, $f_W = 0$ in Eq. 44, maximizing the concentration ratio r.

For this ideal central core model we have

$$r = 1/[1 - f_T(1 - f_U)]. \quad (73)$$

Many of the subsidiary relations derived previously (Stephenson, 1973*a*,*b*) carry over to multinephron models. Thus we have from Eq. 44

$$\partial r/\partial f_T = r^2(1 - f_U)(1 - f_W), \quad (74)$$

$$\partial r/\partial f_U = -r^2 f_T(1 - f_W), \quad (75)$$

and

$$\partial r/\partial f_W = -r^2 f_T(1 - f_U). \quad (76)$$

The approximate analytic solutions *do not* carry over, because these depend on the assumption $J_{2v} = 0$. This is no longer satisfied because the axial flows of loops that turn at $x < 1$ contribute to $J_{2v}(x)$ in the segment in which they turn. It is not assumed that equilibration occurs for each individual solute between DHL, CD, and core; thus, in general

$$c_{ik} \neq c_{ck}, i \in S_1 \cup S_2 \cup S_3. \quad (77)$$

Eqs. 69–71 provide the basis for extending concentration by passive mixing of salt and urea (Stephenson, 1972, 1973*b*, Stephenson et al. 1974; Kokko and Rector, 1972) to multinephron models of the medulla. It should be noted that Eq. 73 obtains not only for the medulla overall, but for any segment between papilla and medulla level x. In particular it holds for the inner medulla.

As the canonical mass balance Eqs. 44 and 73 are written it appears that f_T and f_U are independent variables. This, of course, is not strictly true; fluid which traverses the collecting duct must first pass through more proximal segments of the nephron. For any nephron we have

$$F_{3k}(1) = F_{1k}(0) - T_{1k} - T_{2k} - T_{7k} - T_{3k}, \tag{78}$$

when T_{7k} is transport out of the distal nephron. Summing over k, we obtain

$$F_{3M}(1) = F_{1M}(0) - T_{1M} - T_{2M} - T_{7M} - T_{3M}, \tag{79}$$

if $T_{1M} = T_{7M} = T_{3M} = 0$, then we have

$$F_{3M}(1) = F_{1M}(0) - T_{2m}. \tag{80}$$

Eqs. 78–80 hold for an assemblage of nephrons. By definition the fractional urine flow is

$$f_U \equiv F_{3v}(1)/[F_{1v}(1) + F_{3v}(1)] \tag{81}$$

$$= F_{3v}(1)\, c_{1M}(1)/[F_{1v}(1)\, c_{1M}(1) + F_{3v}(1)\, c_{1M}(1)]. \tag{82}$$

From Eqs. 80 and 82, and $c_{1M} \cong c_{3M}$,

$$f_U = [F_{1v}(0)\, c_{pM} - T_{2M}]/[F_{1v}(1)\, c_{1M}(1) + F_{3v}(1)\, c_{1M}(1)], \tag{83}$$

or

$$f_U = (1 - f_U)(1 - f_T); \tag{84}$$

Eq. 84 can be solved for f_U to give

$$f_U = (1 - f_T)/(2 - f_T). \tag{85}$$

On substitution of Eq. 84 in 44, we obtain

$$r = (2 - f_T)/[2 - f_T(2 - f_W)]. \tag{86}$$

As $f_W \to 0$, Eq. 86 becomes

$$r = 0.5 + 0.5/(1 - f_T). \tag{87}$$

Under these assumptions then, the concentration ratio r, depends on fractional transport out of AHL only. In general, of course, $T_{1M} \neq 0$, both because of DHL solute permeability and because some loops of Henle turn before reaching the papilla. Likewise in general there is solute transport out of distal nephron and collecting duct. The effect of the distal transport is to cause the concentration ratio to vary between a lower limit set by Eq. 87 and the upper limit of $1/(1 - f_T)$. Effectively, Eq. 85 sets an upper limit on f_U, and hence a lower bound on the concentration.

DISCUSSION

The main general conclusion to be drawn from the above analysis is that the concepts developed from the analysis of generic single nephron systems carry over essentially

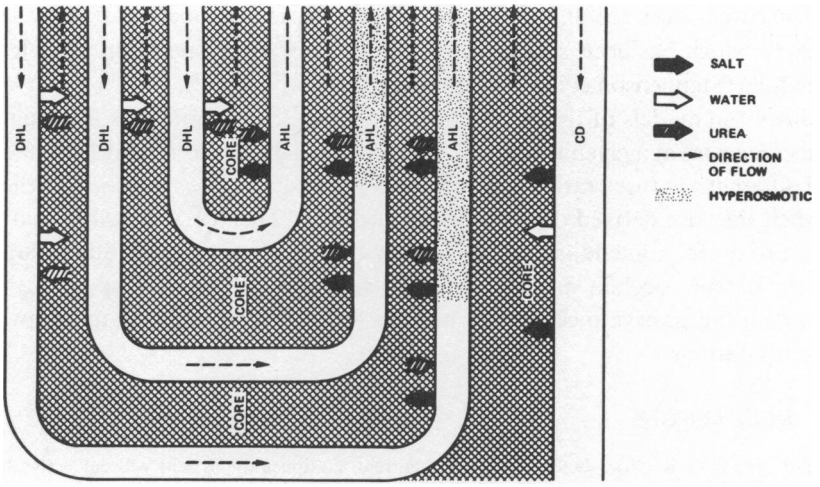

FIGURE 3 Multistage control core model. Note the possible reversal of urea flow in the AHL of loops that descend to the papilla.

unchanged into multinephron models in which an assemblage of tubules and capillaries exchange. In particular, the concentration ratio of papillary structures relative to plasma depends on the fractional solute transported out of the AHL system, the fractional urine withdrawal, and the efficiency of the vascular exchanger. The last is simply defined as W/T_2' where W/c_{pM} is the free water generated by the medulla and T_2' is the effective AHL source. If $W = 0$, then overall the medulla returns isotonic reabsorbate to the systemic circulation. If $W > 0$, true for finite permeabilities, then the reabsorbate is hypertonic.

The general conservation equations apply whether models concentrate by water extraction, solute cycling, or a combination of the two. The requirement for concentration by solute cycling alone is that at every medullary level the total water extraction $T_{1v}(x) + T_{2v}(x) + T_{3v}(x) = 0$. This seems highly unlikely. With concentration in total or part by water extraction the capillaries and interstitium become an integral part of the counterflow system. As capillary solute permeabilities become large it is our hypothesis that in multinephron models as well as single nephron models the vascular interstitial space can be replaced by a "central core" (Fig. 3) closed at the papillary end and open at the cortico-medullary junction. In its most simple operation, solute supplied to this core by the AHL system induces water extraction from the DHL, CD system and so generates a counterflow up the core. In ideal operation this counterflowing solution expands to isotonicity against the inflowing DHL, CD system and a limiting maximum operation is attained. This concentration depends only on fractional transport out of AHL and fractional urine flow or withdrawal from the system.

Analysis of the conservation relations for multisolute central core models shows that concentration of individual solutes in the DHL and CD systems will in general

differ from core concentrations. This provides the basis for concentration by salt and urea mixing which has been studied quantitatively for single nephron models of the inner medulla (Stephenson et al, 1974; Stewart and Valtin, 1972).

Multinephron models of the passive mechanism will clearly have some qualitative differences because at a given medullary depth AHL can have different total osmolalities and different salt/urea ratios depending on the medullary depth to which the DHL from which they are derived descend before turning. Thus, it is possible that in the outer part of the inner medulla some AHL may be supplying salt and others supplying urea to the passive mechanism. Intuitively, it seems clear that this type of cascading will facilitate the passive mechanism, but any quantitative estimate must await detailed computations.

REFERENCES

KOKKO, J. P., and F. C. RECTOR, JR. 1972. Countercurrent multiplication system without active transport in inner medulla. *Kidney Int.* **2**:214.

STEPHENSON, J. L. 1972. Concentration of urine in a central core model for the renal counterflow system. *Kidney Int.* **2**:85.

STEPHENSON, J. L. 1973*a*. Concentrating engines and the kidney. I. Central core model of the renal medulla. *Biophys. J.* **13**:512.

STEPHENSON, J. L. 1973*b*. Concentrating engines and the kidney. II. Multisolute central core systems. *Biophys. J.* **13**:546.

STEPHENSON, J. L., R. MEJIA, and R. P. TEWARSON. 1976. Model of solute and water movement in the whole kidney. *Proc. Natl. Acad. Sci. U.S.A.* **73**:252.

STEPHENSON, J. L., R. P. TEWARSON, and R. MEJIA. 1974. Quantitative analysis of mass and energy balance in non-ideal models of the renal counterflow system. *Proc. Natl. Acad. Sci. U.S.A.* **71**:1618.

STEWART, J., and H. VALTIN. 1972. Computer simulation of osmotic gradient without active transport in renal inner medulla. *Kidney Int.* **2**:264.