CONCENTRATING ENGINES AND THE KIDNEY

II. MULTISOLUTE CENTRAL CORE SYSTEMS

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ABSTRACT The analysis of the central core model of the renal medulla is extended to multisolute systems. It is shown that total solute concentration obeys the same differential equations for core and ascending limb as in a single solute system. Equations are derived for the concentration of individual solutes. Application of these equations to a two solute system shows that a central core system can concentrate with all transport being down a concentration gradient. This analysis applied to the renal medulla shows that mixing of urea from the collecting duct (CD) and salt from the loop of Henle in the central core of the inner medulla contributes to the concentration of urine during antidiuresis. It also sets criteria for completely passive function of the loop in the inner medulla, but whether these are satisfied cannot be determined from present experimental data.

INTRODUCTION

In the preceding paper (Stephenson, 1973, herein referred to as I) we developed a central core model of the renal medulla in which descending Henle's limb (DHL), ascending Henle's limb (AHL), and CD are viewed as grouped around a central vascular core formed by the vasa recta (VR). These are regarded as so highly solute permeable that they form a single tube, closed at the loop or papillary end and open at the end corresponding to the corticomedullary junction. The behavior of this system for a single solute was analyzed.

In this paper the analysis is extended to multisolute systems. In many ways the behavior of the multisolute system is analogous to that of the single solute system, because the sum of the concentrations of the solutes behaves as if it were a single solute. In one way, however, the single and multisolute systems behave very differently. For either system to concentrate there must be net total solute transport out of the ascending limb (see I). If there is any outflow from the CD (i.e., any urine flow), mass balance requires that the osmolality of the ascending limb be less than that of the core. In a single solute system this means the transport out of the AHL

occurs against a concentration gradient, but in a multisolute system this is not necessarily so. If two or more solutes are present in the inflow to the central core system, it can concentrate with all transport being *down* a concentration gradient.

Specifically, it is shown that if the inflows to DHL and CD have the same total osmolality, but the inflow to DHL has salt as the principal solute and that to CD has urea as the principal solute, then salt supplied to the core from AHL and urea from CD can give a mixture of salt and urea in the core, whose salt concentration is less than the salt concentration in Henle's loop and whose urea concentration is less than the urea concentration in CD. As a result transport of both salt and urea will be down a concentration gradient, and given suitable permeabilities of DHL, AHL, and CD, the central core model can concentrate with entirely passive transport.

This theoretical prediction of the central core model suggests a possible solution of the long-standing problem of the origin of the concentration gradient in the inner medulla. There is no doubt that active salt transport out of the thick AHL occurs in the outer medulla. The early distal fluid is hypotonic (Wirz, 1956; Gottschalk and Mylle, 1959) and active salt transport has now been unequivocally demonstrated in thick AHL of the isolated rabbit tubule (Burg, 1972; Rocha and Kokko, 1972). In the inner medulla, however, split drop (Marsh and Solomon, 1965) and perfusion studies (Morgan and Berliner, 1968) have failed to demonstrate active transport out of thin AHL. In an earlier attempt to solve this problem, Pinter and Shohet (1963) suggested that if exchange between interstitium and VR were included in the model of the medulla, the concentration profile in the inner medulla could be generated by passive transport alone. Simulation with an analogue computer appeared to support this idea, but analytic investigation (Stephenson, 1965) revealed a discontinuity in the interstitial concentration at the junction of inner and outer medulla which had been overlooked in the computer simulation. Further analytical investigation (Kelman et al., 1966; Stephenson, 1966) sharpened this result and showed that large classes of single solute systems could not concentrate by passive transport alone. Subsequently, Marumo et al. (1967) included salt, water, and urea movement in an analogue simulation similar to that of Pinter and Shohet. Their profiles show increasing concentration in the inner medulla with no active salt transport in AHL, but they do not show the requisite jump discontinuity in the sodium profile of the interstitium, nor is the origin of the requisite solute source out of AHL obvious (see Marsh, 1971 for further discussion of these papers). Despite the mathematical problems uncovered in its detailed analysis, the Pinter and Shohet model greatly stimulated thinking about the role of the VR in the concentrating mechanism.

It has long been recognized that urea plays an integral role in generating the concentration gradient in the inner medulla (see Schmidt-Nielsen, 1970, for a comprehensive recent colloquy), entering the medulla from the CD, where it is trapped by the VR countercurrent exchanger (Berliner et al., 1958), so developing a high urea concentration. It has also long been recognized that counterflow systems can concentrate by passive mixing, given suitable membrane permeabilities. This was pointed

out by Kuhn and Ryffel (1942) and demonstrated by them in model sucrose and phenol systems. They also suggested that the kidney might utilize the mechanism in some way for concentration, but Kuhn did not develop the idea in his later papers (Hargitay and Kuhn, 1951: Kuhn and Ramel, 1959, *a*, *b*). Subsequently, Niesel and Röskenbleck (1965, 1970) specifically extended the ideas of Kuhn and Ryffel to salt and urea mixing in the renal medulla, in a model directed primarily toward the mechanism of urea concentration. None of the earlier models, however, incorporated urea into the concentrating mechanism in the essential role *predicted* by the central core model: namely, that urea entry into the core induces a secondary salt source in the thin AHL. It is this secondary source that supplies the additional solute necessary for concentration.

The mechanism by which this source is induced is salt and urea mixing in the central core and the subsequent volume expansion of the mixture. Thus, as urea enters the core from CD, it increases the osmolality of the core; if the DHL is relatively urea impermeable and water permeable, this causes water to move by osmosis from DHL to core. The resulting volume expansion of the solution in the core (*a*) dilutes both the salt and urea concentrations in the core, and (*b*) generates a counterflow between core and DHL and CD. The concomitant volume contraction of DHL fluid increases salt concentration in DHL. Because of reversal of flow at the loop the salt concentration in the core falls below that of AHL and salt can diffuse passively out of AHL into the core. If AHL is relatively permeable to salt and impermeable to water, this outward diffusion generates the outward solute source in the AHL, necessary for concentration (see I) in the inner medulla. Because of the solute mixing in the central core, the free energy of the outflow of the inner medulla is less than the free energy of the inflow. Hence, the model satisfies the laws of thermodynamics.

The qualitative and some of the quantitative features of concentration by salt and urea mixing in the central core model have been described before (Stephenson, 1972 *a*, *b*, *c*). The detailed theory developed in this paper establishes unequivocally that, in principle, the concentration profiles of the inner medulla could be generated by salt and urea mixing, with no active transport out of the thin AHL, but it is not yet established that experimental data satisfy the quantitative criteria of the theory.

DIFFERENTIAL EQUATIONS FOR TOTAL SOLUTE CONCENTRATION

The equations for a system of n flow tubes and m solutes are (see I):

$$dF_{ik}/dx = -\sum_j J_{ij,k}, \quad 1 \leq i \leq n, \quad 1 \leq k \leq m, \tag{1}$$

$$dF_{iv}/dx = \sum_j J_{ij,v}, \quad 1 \leq i \leq n, \quad 1 \leq k \leq m, \tag{2}$$

where $J_{ij,k} = J_{aij,k}B_{ij}$ and $J_{ij,v} = J_{aij,v}B_{ij}$. Summing Eqs. 1 over k, we obtain

$$\sum_k (dF_{ik}/dx) = -\sum_k \sum_j J_{ij,k}; \tag{3}$$

from Eq. 3

$$(\mathrm{d}/\mathrm{d}x)\sum_k F_{ik} = -\sum_j \sum_k J_{ij,k}\,. \tag{4}$$

The total axial solute flux is

$$\sum_k F_{ik} = \sum_k [F_{iv}c_{ik} - D_{ik}(\mathrm{d}c_{ik}/\mathrm{d}x)]. \tag{5}$$

If the diffusion coefficients D_{ik} center around some mean value D_{iM}, i.e. $D_{ik} = D_{iM} + \epsilon_{ik}$, we have

$$\sum_k F_{ik} = F_{iv}\sum_k c_{ik} - D_{iM}(\mathrm{d}/\mathrm{d}x)\sum_k c_{ik} - \sum_k \epsilon_{ik}(\mathrm{d}c_{ik}/\mathrm{d}x);$$

or

$$F_{iM} = F_{iv}c_{iM} - D_{iM}(\mathrm{d}c_{iM}/\mathrm{d}x), \tag{6}$$

where $F_{iM} = \sum_k F_{ik}$ and $c_{iM} = \sum_k c_{ik}$, provided $\sum_k \epsilon_{ik}\,\mathrm{d}c_{ik}/\mathrm{d}x \ll F_{iv}c_{iM} - D_{iM}\,\mathrm{d}c_{iM}/\mathrm{d}x$. Substitution of Eq. 6 into Eq. 4 gives

$$-D_{iM}(\mathrm{d}^2c_{iM}/\mathrm{d}x^2) + [\mathrm{d}(F_{iv}c_{iM})/\mathrm{d}x] = -J_{iM}\,, \tag{7}$$

where $J_{iM} = \sum_j \sum_k J_{ij,k}$. For each tube Eq. 7 is identical with that for a single solute. If we neglect diffusion terms we have

$$(\mathrm{d}/\mathrm{d}x)(F_{iv}c_{iM}) = -J_{iM}\,. \tag{8}$$

If we introduce the same assumptions we made in analyzing the single solute system, namely, the descending limb and CD are so highly water permeable that $c_{1M}(x) = c_{3M}(x) = c_{4M}(x)$ and the ascending limb is so water impermeable that $F_{2v}(x) = -F_{1v}(L)$, the derivations go through as in part I. In particular, we have

$$[F_{1v}(L) + F_{3v}(L)][\mathrm{d}c_{4M}(x)/\mathrm{d}x] = J_{2M}\,, \tag{9}$$

and

$$F_{1v}(L)[\mathrm{d}c_{2M}(x)/\mathrm{d}x] = J_{2M}\,. \tag{10}$$

All results which followed from Eqs. 69 and 70 of part I, which are identical with Eqs. 9 and 10, remain valid. These are all the results of I except the detailed computation of concentration profiles and thermodynamic potential differences.

CONCENTRATIONS OF INDIVIDUAL SOLUTES

Solution of the Eqs. 1, 2, and 8 except in very special cases must be done numerically. As for single solute systems, however, certain important relations are independent of the mechanism of transport. From Eqs. 1 and 8 we always have

$$\frac{F_{ik}(x_2) - F_{ik}(x_1)}{F_{iM}(x_2) - F_{iM}(x_1)} = \frac{\int_{x_1}^{x_2} J_{ik}\,\mathrm{d}x}{\int_{x_1}^{x_2} J_{iM}\,\mathrm{d}x}\,. \tag{11}$$

In the central core at the closed end, all axial flows are zero; i.e. $F_{4k}(L) = 0$, and $F_{4M}(L) \equiv \sum_k F_{4k}(L) = 0$ and Eq. 11 becomes

$$F_{4k}(x)/F_{4M}(x) = \frac{\int_x^L J_{4k}(x)\,dx}{\int_x^L J_{4M}(x)\,dx}. \tag{12}$$

If the diffusional terms in $F_{4k}(x)$ and $F_{4M}(x)$ are small relative to the bulk flow terms (an assumption which is reasonably valid as $x \to 0$, but which must be examined closely as $x \to L$), Eq. 12 becomes

$$c_{4k}(x)/c_{4M}(x) = \frac{\int_x^L J_{4k}(x)\,dx}{\int_x^L J_{4M}(x)\,dx}. \tag{13}$$

Eqs. 1 and 2 can be cast into what is frequently a more useful form. They can be rewritten

$$dF_{ik}/dx = -J_{ik}, \tag{14}$$

$$dF_{iv}/dx = -J_{iv}, \tag{15}$$

where $J_{ik} = \sum_j J_{ij,k}$ and $J_{iv} = \sum_j J_{ij,v}$. On substituting $F_{ik} = F_{iv}c_{ik}$, we derive from Eqs. 14 and 15

$$dc_{ik}/dx = (-J_{ik} + J_{iv}c_{ik})/F_{iv}, \tag{16}$$

and from Eqs. 8 and 15

$$dc_{iM}/dx = (-J_{iM} + J_{iv}c_{iM})/F_{iv}. \tag{17}$$

Eqs. 16 and 17 must be applied with some caution because in the central core $F_{4v}(L) = 0$, which gives rise to a singularity. If $F_{iv}(x) \neq 0$, and J_{ik} and J_{iv} are functions only of the c_{ik}, then Eq. 16 and the equation

$$dF_{iv}/dx = -J_{iv}, \tag{18}$$

give an autonomous set of first-order differential equations. The volume flows F_{iv} can be eliminated from Eqs. 16 and 17 to give the equation

$$dc_{ik}/dc_{iM} = (-J_{ik} + J_{iv}c_{ik})/(-J_{iM} + J_{iv}c_{iM}). \tag{19}$$

For the ascending limb (if it is impermeable to water) we have from Eq. 16

$$dc_{2k}/dx = -J_{2k}/F_{2v}. \tag{20}$$

CONCENTRATION IN TWO SOLUTE SYSTEMS

To focus the above analysis on a specific (highly idealized) example, let us consider a two solute system in which pure solution of one solute at concentration $c_{11}(0)$ enters the descending limb, and pure solution of a second solute at concentration $c_{32}(0)$ enters the CD, the osmolality of the two solutions being the same. Let the descending limb be water permeable, solute impermeable; let the ascending limb be permeable to the first solute, impermeable to the second, and water impermeable; let the CD be water permeable, permeable to the second solute, and impermeable to the first. We will suppose that there is transport J_{21} of the first solute out of the ascending limb and transport J_{32} of the second solute out of the CD. We will also suppose that $c_{1M} \cong c_{4M} \cong c_{3M}$ (in a more realistic model account must be taken of actual reflection coefficients). Only in the central core does the solution contain both solutes, so the above assumptions give

$$c_{11}(x) = c_{32}(x) = c_{41}(x) + c_{42}(x) = c_{4M}(x). \tag{21}$$

From Eqs. 13 and 21

$$c_{42}(x)/c_{4M}(x) = c_{42}(x)/c_{32}(x) = \frac{\int_x^L J_{42}(x)\,dx}{\int_x^L J_{4M}(x)\,dx}, \tag{22}$$

or

$$c_{42}(x)/c_{32}(x) = T_{32}(x)/[T_{32}(x) + T_{21}(x)], \tag{23}$$

where

$$T_{32}(x) = \int_x^L J_{32}(x)\,dx = -\int_x^L J_{42}(x)\,dx, \tag{24}$$

and

$$T_{21}(x) = \int_x^L J_{21}(x)\,dx = -\int_x^L J_{41}(x)\,dx. \tag{25}$$

It is clear from Eq. 23 that if $T_{21}(x) > 0$ and $T_{32}(x) > 0$ then $c_{42}(x) < c_{32}(x)$. Thus, everywhere transport of the second solute out of the CD occurs down a chemical potential gradient.

The interesting question arises: can the transport of solute out of the ascending limb also be entirely down a chemical potential gradient? We have

$$\frac{c_{41}(x)}{c_{21}(x)} = \frac{c_{41}(x)}{c_{2M}(x)} = \frac{c_{41}(x)}{c_{4M}(x)} \cdot \frac{c_{4M}(x)}{c_{2M}(x)}, \tag{26}$$

or

$$\frac{c_{41}(x)}{c_{21}(x)} = \frac{T_{21}(x)}{T_{32}(x) + T_{21}(x)} \frac{c_{4M}(x)}{c_{2M}(x)}. \tag{27}$$

From part I, using an obvious modification of Eq. 136, we have

$$\frac{c_{4M}(x)}{c_{2M}(x)} = \frac{1 - f_U}{1 - r(x)f_U}, \tag{28}$$

where $r(x) = c_{4M}(L)/c_{4M}(x)$. For $c_{41}(x) < c_{21}(x)$, we obtain from Eqs. 27 and 28 the condition

$$\frac{T_{32}(x)}{T_{21}(x)} + 1 > \frac{1 - f_U}{1 - r(x)f_U}, \tag{29}$$

which is equivalent to

$$\frac{T_{32}(x)}{T_{21}(x)} > \frac{f_U[r(x) - 1]}{1 - r(x)f_U}. \tag{30}$$

As $f_U \to 0$ or $r(x) \to 1$, the condition 21 can always be satisfied. Likewise, if f_U and r are given, the condition can be satisfied if one is free to choose $T_{32}(x)$. Thus, a central core engine can be made to concentrate with all transport being down a concentration gradient. If membrane permeabilities can be freely assigned, such a system could concentrate using only permselective membranes and passive transport.

The above system does not violate thermodynamic principles. The outflow of the system has *less* free energy than the inflow because of the mixing in the central core. Each solute in the solution leaving the central core is less concentrated than in the entering solutions as is the solution leaving in the ascending limb. The overall free energy decrease equals the free energy loss because of the transmembrane transport down a chemical potential (a detailed proof of this statement will be given in a later paper). As we noted in the introduction, the principle of concentrating by mixing through permselective membranes was first enunciated by Kuhn and Ryffel in their 1942 paper (Kuhn and Ryffel, 1942).

An exact analytical analysis of the two solute system is not possible, but an approximate analysis can be carried out. Let the above two solutes be salt and urea and let them exchange with the central core by passive diffusion only. In order to simplify the analysis we will again suppose the solution entering DHL contains salt as the only solute and that entering the CD contains urea as the only solute. This is highly idealized from the actual situation and optimizes the operation of the system. Then we have

$$J_{2M} = h_{24,s}(c_{2M} - c_{4s}), \tag{31}$$

$$J_{3M} = h_{34,u}(c_{3M} - c_{4u}), \tag{32}$$

$$c_{3M} \cong c_{4M} = c_{4u} + c_{4s}, \; c_{2M} = c_{2s}, \; c_{3M} = c_{3u}, \tag{33}$$

where $h_{24,s}$ is the permeability of the AHL for urea and $h_{34,u}$ is the permeability of the CD for urea. The differential equations for ascending limb and central core are:

$$[F_{1v}(L) + F_{3v}(L)](dc_{4M}/dx) = h_{24,s}(c_{2M} - c_{4s}), \tag{34}$$

and

$$F_{1v}(L)(dc_{2M}/dx) = h_{24,s}(c_{2M} - c_{4s}). \tag{35}$$

Eq. 13 becomes

$$\frac{c_{4s}}{c_{4M}} = \frac{h_{24,s}\int_x^L (c_{2M} - c_{4s})\,dx}{h_{24,s}\int_x^L (c_{2M} - c_{4s})\,dx + h_{24,u}\int_x^L (c_{4M} - c_{4u})\,dx}. \tag{36}$$

From Eqs. 33, 35, and 36 we obtain at x

$$\frac{c_{4s}}{c_{4M}} = \frac{F_{1v}[c_{2M}(L) - c_{2M}]}{F_{1v}[c_{2M}(L) - c_{2M}] + h_{34,u}\int_x^L c_{4s}\,dx}. \tag{37}$$

Eqs. 34 and 35 give the relation (see Eq. 101, part I)

$$c_{4M}(x) = (1 - f_U)c_{2M}(x) + f_U c_{4M}(L). \tag{38}$$

To solve the above system we define the auxiliary variable $\alpha(x) \equiv c_{4s}/c_{2M}$. Then Eq. 35 becomes

$$F_{1v}(L)(dc_{2M}/dx) = h_{24,s}(1 - \alpha)c_{2M}. \tag{39}$$

Only if $0 \leq \alpha(x) < 1$ are dc_{2M}/dx and dc_{4M}/dx positive and $\alpha(x)$ physically realizable, and we will assume $\alpha(x)$ is so restricted. Using Eq. 38 and the definition of α and the boundary condition $c_{2M}(L) = c_{4M}(L)$, we obtain from Eq. 37

$$\alpha(x) = [1 - f_U + f_U c_{2M}(L)/c_{2M}] \Big/ \left\{1 + \frac{h_{34,u}\int_x^L \alpha c_{2M}\,dx}{F_{1v}(L)[c_{2M}(L) - c_{2M}]}\right\}. \tag{40}$$

Eq. 39 integrates to give

$$c_{2M}(L)/c_{2M}(x) = \exp\left[\frac{h_{24,s}}{F_{1v}(L)}\int_x^L (1 - \alpha)\,dx\right]. \tag{41}$$

We shall use an iterative technique to solve Eqs. 40 and 41. We shall first estimate $\alpha(x)$, compute $c_{2M}(L)/c_{2M}(x)$ from Eqs. 39 or 41, and then use Eq. 40 to compute a new value of $\alpha(x)$. This value substituted into Eq. 41 or Eq. 39 leads to a new value of $c_{2M}(L)/c_{2M}(x)$ and so on. In the Appendix we show that if the initial esti-

mate is $\alpha_0(x)$, the first iteration $\alpha_1(x)$, and the second iteration is $\alpha_2(x)$, then the true solution is bounded by the successive iterates provided either the condition

$$\alpha_0(x) > \alpha_2(x) > \alpha_1(x) \tag{42}$$

or the condition

$$\alpha_0(x) < \alpha_2(x) < \alpha_1(x) \tag{43}$$

is satisfied. At $x = L$ the right-hand side of Eq. 40 becomes indeterminate, but as $x \to L$ it approaches the limit α_L given by

$$\alpha_L = \frac{h_{24,s}(1 - \alpha_L)}{h_{24,s}(1 - \alpha_L) + h_{34,u}\alpha_L}. \tag{44}$$

(Eq. 44 is most easily derived from Eq. 36 by use of L'Hospital's rule and the limiting condition $c_{2M}(x)/c_{4M}(x) \to 1$ as $x \to L$.) Only one root of Eq. 44 is both positive and less than 1, that is

$$\alpha_L = (h_{24,s})^{1/2}/[(h_{24,s})^{1/2} + (h_{34,u})^{1/2}]. \tag{45}$$

As the first estimate we will take the serendipitous guess

$$\alpha_0(x) = [1 - f_U + f_U c_{2M}(L)/c_{2M}(x)]\alpha_L = c_{4M}(x)\alpha_L/c_{2M}(x). \tag{46}$$

Substituted into Eq. 39, Eq. 46 leads to the solution

$$c_{2M}(x) = B/A + [c_{2M}(L) - B/A] \exp[-A(L - x)], \tag{47}$$

where

$$A = h_{24,s}[1 - (1 - f_U)\alpha_L]/F_{1v}(L) \tag{48}$$

and

$$B = h_{24,s}f_U\alpha_L c_{2M}(L)/F_{1v}(L). \tag{49}$$

For $f_U = 0$, we have from Eq. 46, $\alpha_0(x) = \alpha_L$ and from Eq. 47

$$c_{2M}(x) = c_{2M}(L) \exp[-A(L - x)], \tag{50}$$

where $A = h_{24,s}(1 - \alpha_L)/F_{1v}(L)$. Substitution of the solutions Eqs. 46 and 50 into Eq. 40, with $f_U = 0$, again gives $\alpha(x) = \alpha_L$. Thus for $f_U = 0$, $\alpha(x) = \alpha_L$ is an exact solution.

In general when $f_U \neq 0$, α_0 and the first iteration α_1 differ except at $x = L$, where both equal α_L. The computation of α_1 from Eq. 40 is simplified by noting that from Eqs. 46 and 40 the ratio of the initial estimate to the first iteration is given by

$$\frac{\alpha_0(x)}{\alpha_1(x)} = \alpha_L \left\{ 1 + \frac{h_{34,u}\alpha_L \int_x^L c_{4M}\, dx}{F_{1v}(L)[c_{2M}(L) - c_{2M}(x)]} \right\} \tag{51}$$

where we have used the relation $\alpha_0 c_{2M} = \alpha_L c_{4M}$. Using Eq. 47, we find

$$F_{1v}[c_{2M}(L) - c_{2M}(x)] = F_{1v}[c_{2M}(L) - B/A]\{1 - \exp[-A(L - x)]\}, \quad (52)$$

and using Eqs. 47 and 38, we obtain

$$\int_x^L c_{4M}\, dx = E(L - x) + [(1 - f_U)/A][c_{2M}(L) - B/A] \times \{1 - \exp[-A(L - x)]\}, \quad (53)$$

where

$$E = (1 - f_U)(B/A) + f_U c_{2M}(L). \quad (54)$$

Substitution of Eqs. 53 and 52 into Eq. 51 permits calculation of $\alpha_1(x)$.

In Fig. 1, are shown c_{4M}, c_{2M}, and c_{4s} for $f_U = 0.05$, $c_{2M}(L) = 10$, $L = 1$, $h_{24,s} = h_{24,u} = 5$, and $F_{1v}(L) = 1.0$, in the region $0.5 < x < 1.0$. In Table I are shown α_0, α_1, and α_2 vs. x. It can be seen that in the region $0.5 \leq x \leq 1$ the difference between $\alpha_0(x)$ and the true value of $\alpha(x)$, which lies between $\alpha_0(x)$ and $\alpha_1(x)$, is less than $0.02(1 - x)$. Substituted into Eq. 39 this error estimate shows that $c_{2M}(x)$ and $c_{4M}(x)$ differ from their true values by a factor lying between 1 and 1.013.

The above analysis clearly shows that it is possible for central core systems to concentrate by passive mixing, but it remains to be demonstrated that the inner

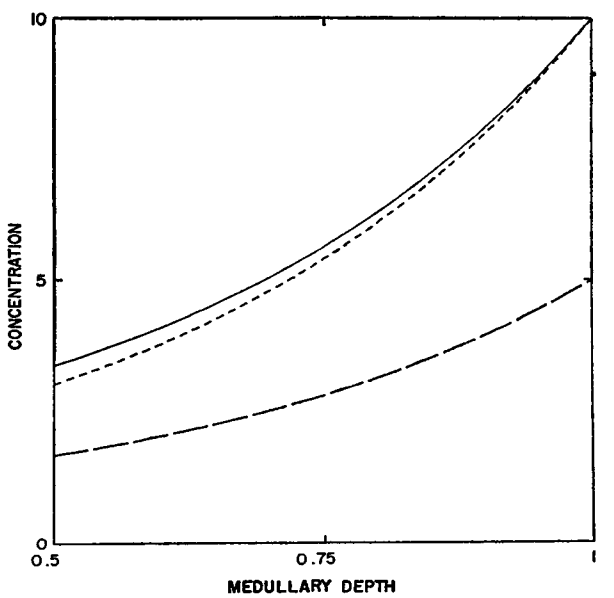

FIGURE 1 Concentration profiles for passive mixing. The upper curve is total core concentration; the middle, AHL-salt concentration, and the lower, core salt concentration. Core urea is the difference between total core concentration and core salt concentration.

TABLE I

COMPARISON OF INITIAL ESTIMATE, FIRST ITERATION, AND SECOND ITERATION OF $\alpha(x)$

Medullary depth x	Initial estimate α_0	First iteration α_1	Second iteration α_2
0.0000000	0.6893912	0.6341310	0.6758810
0.1000000	0.6570585	0.6103210	0.6407673
0.2000000	0.6272124	0.5881943	0.6102503
0.3000000	0.6004690	0.5683836	0.5842412
0.4000000	0.5771371	0.5512507	0.5625411
0.5000000	0.5572507	0.5369034	0.5448006
0.6000000	0.5406352	0.5252472	0.5305777
0.7000000	0.5269822	0.5160492	0.5194079
0.8000000	0.5159162	0.5089995	0.5109175
0.9000000	0.5070563	0.5037602	0.5045147
0.9100000	0.5062655	0.5033229	
0.9200000	0.5055025	0.5029001	
0.9300000	0.5047571	0.5024914	
0.9400000	0.5040287	0.5020964	
0.9500000	0.5033172	0.5017150	
0.9600000	0.5026221	0.5013469	
0.9700000	0.5019432	0.5009915	
0.9800000	0.5012801	0.5006488	
0.9900000	0.5006325	0.5003184	
1.00	0.5	0.5	0.5

medulla of the kidney depends solely on mixing for concentration. In the above example, for instance, approximately the same amount of urea as salt must be supplied to the central core. One can calculate that the volume flow in the CD at $x = 0.5$ is about 2.5 $F_{1v}(L)$, a totally unrealistic value. By increasing the ratio $h_{24,s}/h_{34,u}$ and reducing f_U, more plausible values for $F_{3v}(0.5)$ can be obtained, but the availability of urea is clearly a limiting factor in the operation of the system. This will be analyzed in the following section.

ROLE OF SALT AND UREA MIXING IN THE CONCENTRATION OF URINE

It is experimentally established that urea leaves the CD, part of it entering Henle's loop to be recycled and part of it entering the VR to be returned to the systemic circulation (Schmidt-Nielsen, 1970). In so far as the central core model is a valid representation of the renal medulla, the above analysis shows that urea entering the central core will induce water withdrawal from the descending limb and CD. This water entering the core will dilute the salt in the core and depress it below the concentration in DHL, and at least in the loop, where the DHL flow enters AHL, the concentration in AHL will be greater than in the vascular core. This decrease of NaCl concentration in the core will certainly decrease back leak of NaCl into Henle's

loop in both DHL and AHL. By Eq. 79 of paper I the concentration ratio is given by

$$r = \frac{1}{1 - T_{2M}/[F_{1M}(0) - T_{1M} + F_{3M}(0) - T_{3M}]}. \tag{55}$$

Urea entry into the core will cause positive increments in the transport integrals T_{2M}, T_{1M}, and T_{3M}. Each of these increments will increase the concentration ratio. At least in the region of the loop transport of both salt and urea can be down a concentration gradient. That this actually occurs is supported by a recomputation (Stephenson, 1972 *b*) of some of Marsh's data (Marsh, 1970). The idea that urea entry into the inner medulla induces a solute source in the thin AHL is also supported by the experimental observations of Niesel and Röskenbleck (Niesel et al., 1970; Franke et al., 1970).

Present data are not sufficient to determine whether transport throughout the inner medulla is down a concentration gradient as the following analysis shows. For salt transport out of AHL to be passive it is necessary that salt concentration in the core be less than salt concentration in AHL; i.e.

$$\frac{c_{4s}(x)}{c_{2s}(x)} = \frac{c_{4s}(x)}{c_{4M}(x)} \cdot \frac{c_{4M}(x)}{c_{2M}(x)} \cdot \frac{c_{2M}(x)}{c_{2s}(x)} < 1 \tag{56}$$

must be satisfied for all x in the inner medulla. From Eqs. 13 and 23, we have

$$\frac{c_{4s}}{c_{4M}} = \frac{T_{4s}}{T_{4s} + T_{4u}}. \tag{57}$$

Substituting from Eqs. 57 and 38 into Eq. 56 and taking reciprocals, we obtain as the condition for passive transport

$$\left(1 + \frac{T_{4u}}{T_{4s}}\right)\left(\frac{1 - rf_U}{1 - f_U}\right)\left(\frac{c_{2s}}{c_{2M}}\right) > 1. \tag{58}$$

By the general mass balance relations (Eq. 16, paper I), the *net* urea transport into the core is

$$T_{4u} = -(T_{3u} + T_{2u} + T_{1u}). \tag{59}$$

If a fraction f_{ur} of the urea T_{3u} that enters the core from CD is recycled in DHL and AHL, then we have

$$T_{1u} + T_{2u} = -f_{ur}T_{3u}, \tag{60}$$

and

$$T_{4u} = -T_{3u}(1 - f_{ur}). \tag{61}$$

Similarly,

$$T_{4s} = -(T_{1s} + T_{2s} + T_{3s}). \tag{62}$$

Substitution of Eqs. 60 and 62 into relation 58 gives the *necessary* condition for passive transport

$$(1 + r_T)[(1 - rf_U)/(1 - f_U)](c_{2s}/c_{2M}) > 1, \tag{63}$$

where

$$r_T = \frac{T_{3u}(1 - f_{ur})}{T_{1s} + T_{2s} + T_{3s}}. \tag{64}$$

Since $c_{2s}/c_{2M} \leq 1$, in order for Eq. 63 to be satisfied it is necessary that

$$(1 + r_T)[(1 - rf_U)/(1 - f_U)] > 1, \tag{65}$$

which is equivalent to

$$r_T > \frac{f_U(r - 1)}{1 - rf_U}, \tag{66 a}$$

be satisfied. Present data do not permit a critical test of Eq. 63 or even Eq. 66 *a*; but some qualitative discussion is possible. Clearly, if either $f_U \to 0$ or $r \to 1$, Eq. 66 *a* can always be satisfied and the chance of satisfying Eq. 63 is improved. For example, if $r = 3$ (the reader is reminded that all variables are referred to the inner medulla) and $f_U = 0.1$, then in order to satisfy Eq. 66 *a* we must have $r_T > 0.285$, whereas if $r = 3$ and $f_U = 0.01$, $r_T > 0.0202$ is sufficient.

In Eq. 64, T_{3u} the urea transported out of the CD can be no greater than that entering the CD from the distal tubule. The urea entering the CD is made up of that which has never been recycled, that recycled once, twice, etc. If f_1 is the fraction of the filtered urea that makes a first pass through the CD and f_r' is the fraction of that transported out of the CD and recycled via Henle's loops then the total urea entering the CD is

$$F_{3u} = \text{GFR} \cdot [\text{urea}]_p[f_1 + f_1 f_r' + f_1 f_r'^2 + \ldots] \tag{66 b}$$

or

$$F_{3u} = \text{GFR} \cdot [\text{urea}]_p f_1/(1 - f_r'), \tag{67}$$

where $[\text{urea}]_p$ is plasma urea concentration and GFR is glomerular filtration rate. It is usually assumed that about one-half of the filtrated urea is absorbed in the proximal tubule, so $f_1 \simeq \frac{1}{2}$. Measurements in the distal convoluted tubules (de Rouffignac and Morel, 1969) of cortical nephrons indicate that F_{3u} may be up to four times the filtered urea load, implying that overall $f_r' \simeq 0.9$. Since $f_r' = f_r'' f_r'''$, where f_r'' is the fraction of urea entering the CD which enters the core, and f_r''' is the fraction of urea that enters the core that enters Henle's loop, $f_r' \leq f_r''$, and total urea entering the medulla from the CD is greater than $f_r' F_{3u}$. This urea is, however, distrib-

uted between inner and outer medulla in an unknown way. It is not unreasonable to assume that approximately one-half of it enters the inner medulla, which could imply that

$$T_{3u} \simeq 2 \text{ GFR} \cdot [\text{urea}]_p , \tag{68}$$

but certainly Eq. 68 is only an *order of magnitude* estimate.

Any precise estimate of the net salt supplied to the vascular core in the inner medulla is equally difficult. In the above model, the salt transported from AHL to core is

$$T_{2s} = F_{1v}(L)[c_{2s}(L) - c_{2s}(x_b)], \tag{69}$$

where x_b is the junction between inner and outer medulla. If urea entry into AHL is small relative to T_{2s}, then

$$T_{2s} \simeq F_{1v}(L)[c_{2M}(L) - c_{2M}(x_b)]. \tag{70}$$

From Eq. 38 and 68

$$T_{2s} = F_{1v}(L)c_{2M}(L) \frac{r - 1}{r(1 - f_U)} . \tag{71}$$

If $T_{1s} \ll T_{2s}$ then

$$F_{1v}(L)c_{2M}(L) \simeq F_{1v}(x_b)c_{1M}(x_b) \tag{72}$$

and for $f_U \ll 1$

$$T_{2s} \simeq F_{1v}(x_b)c_{1M}(x_b)[(r - 1)/r]. \tag{73}$$

In Eq. 73, $F_{1v}(x_b)c_{1M}(x_b)$ is the total salt load *entering* the inner medulla in DHL. Again, this is not known with any precision, but is probably $\frac{1}{5}$ to $\frac{1}{10}$ the total filtered load. Thus, finally

$$T_{2s} \simeq 0.2 \text{ GFR} \cdot [\text{NaCl}]_p \left[\frac{(r - 1)}{r}\right], \tag{74}$$

where $[\text{NaCl}]_p$ is plasma salt concentration. Substituting from Eqs. 68 and 74 into Eq. 64 and assuming $T_{1s} \ll T_{2s}$ and $T_{3s} \ll T_{2s}$, we obtain

$$r_T \simeq 10 \frac{[\text{urea}]_p}{[\text{NaCl}]_p} (1 - f_{ur}) \frac{r}{r - 1} . \tag{75}$$

From Eqs. 75 and 66 *a* we obtain as a necessary condition for passive function of the inner medulla

$$\frac{f_U(r - 1)^2}{(1 - rf_U)r} < 10(1 - f_{ur}) \frac{[\text{urea}]_p}{[\text{NaCl}]_p} , \tag{76}$$

and since $1 - f_{ur} < 1$

$$\frac{f_U(r-1)^2}{(1-rf_U)r} < 10\,\frac{[\text{urea}]_p}{[\text{NaCl}]_p}. \tag{77}$$

If $[\text{urea}]_p/[\text{NaCl}]_p \simeq 1/50$, then from Eq. 77 we obtain

$$f_U < \frac{0.2r}{(r-1)^2 + 0.2r^2}. \tag{78}$$

If the overall concentration ratio of the inner medulla is 2, then from Eq. 78 we must have $f_U < 0.22$, and for $r = 3, f_U < 0.1$. In the antidiuretic rodent kidney, a concentration ratio of 2 to 3 for the inner medulla, and a ratio of CD flow to DHL plus CD flow of the order of 0.1 is not implausible, but it seems clear that only carefully designed experiments will establish whether enough urea enters the inner medulla from the CD so that NaCl transport out of the thin AHL is *always* down a concentration gradient. It seems equally clear that during antidiuresis enough urea enters the medulla to depress core salt concentration relative to AHL salt concentration. Thus, to any active transport is added a positive diffusive increment. Even in the outer medulla back leak will be reduced, and as shown in I, a reduction in back leak can cause a marked increase in the concentration ratio.

For the inner medulla to function passively by salt and urea mixing it is not only necessary to have enough urea cycled to drive the system, but AHL and CD must have the proper permeabilities. These can be estimated for a given value of r_T from the above model. Thus, we have from Eqs. 57 and 64 and the definition of α

$$\alpha = \frac{1}{1 + r_T/(1 - f_{ur})}. \tag{79}$$

As $x \to L$, we have from Eqs. 45 and 79 if $f_{ur} \ll 1$

$$(h_{24,u})^{1/2}/(h_{24,s})^{1/2} = r_T = c_{2u}(L)/c_{2s}(L). \tag{80}$$

Eq. 80 both gives another estimate of r_T, and also determines the ratio $h_{24,u}/h_{24,s}$ and so α_L. The ratio of urea transport into the core to salt transport into the core as estimated from the ratio of VR urea and salt concentrations at the papilla would be expected to be somewhat higher than that estimated from overall salt and urea transport, because only a fraction of the Henle's loops that enter the inner medulla descend to the papilla. Marsh's data for hamsters (1970) suggest r_T is between 0.2 and 0.3; the data of de Rouffignac and Morel (1969) for *Psammomys* indicate a somewhat lower value, but both are of the same order of magnitude as r_T estimated above.

Given α_L, f_U, and r we can estimate $h_{24,s}$ by Eqs. 47–49. Thus, for $r_T \simeq 0.2$, $\alpha_L = 0.835$. If $f_U = 0.01$ and $r = 3$, we compute $B/A = 0.0474\, c_{2M}(L)$, $A \simeq 2.42$, $h_{24,s}/F_{1v}(L) \simeq 13.7$, $h_{24,u}/F_{1v}(L) \simeq 0.55$.

Even though the above computation is approximate, it is clear that the passive permeability of the AHL for salt must be very high if the system is to function with no active transport. In the above computation we normalized the depth of the inner medulla to 0.5. If the depth were actually 5 mm, $h_{24,s}/F_{1v}(L) = 13.7$ would imply that radio sodium perfused in AHL at the normal flow rate would decrease to 0.25 its initial concentration in a distance of 1 mm. Such a high permeability does not appear to be consistent with the relatively low permeability of thin AHL to sodium reported by Morgan and Berliner (1968), but recently reported transport studies of perfused isolated AHL and DHL of rabbit nephrons appear to support the concept of passive function of the inner medulla (Kokko, 1972 *a*, *b*), and have been so interpreted in a model proposed by Kokko and Rector (1972).

DIURESIS AND ANTIDIURESIS

Additional support for the hypothesis that thin AHL and thick AHL have markedly different transport properties can be obtained from the change in concentration profile between antidiuresis and water diuresis. In antidiuresis, slice studies (Ullrich and Jarausch, 1956; Bray and Preston, 1970), have shown an increasing osmolar gradient from cortex to papilla. During water diuresis a marked change in the shape of the osmolality profile is seen. The gradient increases in the outer medulla, but at the junction of inner and outer medulla abruptly flattens and remains nearly flat throughout the inner medulla. This change in slope can only be accounted for by a change in the solute transport out of AHL between inner and outer medulla. From Eq. 17 we have for the total osmolality in the core

$$dc_{4M}/dx = (-J_{4M} + J_{4v}c_{4M})/F_{4v}. \tag{81}$$

If DHL is relatively solute impermeable,

$$J_{4M} \cong -J_{2M} - J_{3M}; \tag{82}$$

and if AHL is relatively water impermeable,

$$J_{4v} \cong -J_{1v} - J_{3v}. \tag{83}$$

Substituting Eqs. 82 and 83 into Eq. 81 we obtain

$$dc_{4M}/dx = \frac{J_{2M} + J_{3M} - (J_{1v} + J_{3v})c_{4M}}{F_{4v}}. \tag{84}$$

Except at $x = L$, $F_{4v} > 0$, and in addition everywhere F_{4v} is continuous. Eq. 84 shows that dc_{4M}/dx has the sign of $J_{2M} + J_{3M} - (J_{1v} + J_{3v})c_{4M}$. In the outer medulla in water diuresis $dc_{4M}/dx > 0$, and in the inner medulla $dc_{4M}/dx \cong 0$. To account for the discontinuity in slope there must be a discontinuity in $J_{2M} + J_{3M} -$

$(J_{1v} + J_{3v})c_{4M}$. But J_{3M} and J_{3v} are functions of solute concentration in core and CD. These concentrations are continuous. There is no evidence that permeability properties of the CD change from inner to outer medulla. If the DHL is relatively solute impermeable

$$J_{1v} \cong \frac{F_{1v}(0)c_{1M}(0)}{[c_{1M}(x)]^2} \frac{dc_{4M}}{dx}. \tag{85}$$

Thus, $J_{1v} > 0$, in the outer medulla and $J_{1v} = 0$ in the inner medulla. It follows that if $x = B$ is the junction of inner and outer medulla,

$$[dc_{4M}/dx]_{x<B} = [J_{2M}/F_{4v}]_{x<B} - [J_{2M}/F_{4v}]_{x>B} - [J_{1v}c_{4M}/F_{4v}]_{x<B}, \tag{86}$$

or

$$[J_{2M}]_{x<B} - [J_{2M}]_{x>B} = F_{4v}(B)[dc_{4M}/dx]_{x<B} + [J_{1v}c_{4M}]_{x<B}. \tag{87}$$

There is, therefore, a discontinuity in J_{2M} at $x = B$, such that $[J_{2M}]_{x>B} < [J_{2M}]_{x<B}$. A similar argument shows that in antidiuresis any discontinuity in J_{2M} at $x = B$ is small.

Such a discontinuity in J_{2M} during diuresis can only be accounted for by assuming an abrupt change in the transport properties of the AHL between inner and outer medulla. Obviously if the thin AHL can transport only down a concentration gradient this will account for the flattening, because in water diuresis the CD and distal tubule become less permeable to both urea and water. Urea concentration does not rise in the CD and much less enters the core. As a result core [NaCl] rises to the concentration of the DHL. If any transport out of AHL takes place, this reduces AHL salt concentration below that of the core. Thus, diffusive transport of NaCl out of AHL (and DHL) is turned off.

The approximate analytic theory given above shows that as the urea permeability of the CD decreases, for constant salt permeability of the AHL, the gradients dc_{2M}/dx and dc_{4M}/dx, in the inner medulla will flatten. This can be seen from Eq. 39 because (from Eq. 45) the product

$$h_{24,s}(1 - \alpha_L) = h_{24,s}(h_{34,u})^{1/2}/[(h_{24,s})^{1/2} + (h_{34,u})^{1/2}], \tag{88}$$

decreases monotonically with $h_{34,u}$. If $h_{34,u} = 0$, then we have $\alpha = 1$ and $dc_{2M}/dx = 0$.

The theory predicts concomitant flattening of the gradients for both salt and urea with decreasing $h_{34,u}$. Such changes have been found experimentally (Atherton et al., 1971, 1972) with intravenous infusion of lysine-vasopressin into water-loaded rats, and can be interpreted as caused by the vasopressin decreasing the urea permeability of the CD.

In the past the flattening of the gradient in the inner medulla during diuresis has

been attributed to both increased water uptake and increased vascular washout. Although these will both decrease concentration throughout the medulla, neither can account for the change in shape of the osmolality profile. The analysis given above will. An interesting prediction of the above theory is that in water diuresis dc_{4M}/dx can be negative in the inner medulla if $J_{2M} < (J_{1v} + J_{3v})c_{4M}$. This certainly can occur if $J_{2M} = 0$.

Another interesting prediction of the theory is that in going from antidiuresis to diuresis the degree of solute cycling can change markedly. Thus in diuresis, with no urea entering the core, salt concentration in the core will be at least slightly greater than that in DHL (see I) and some salt recycling will occur. In antidiuresis, when urea entry into the core depresses core salt concentration relative to DHL salt concentration, at least in the inner medulla salt will enter the core from DHL and salt cycling will decrease.

DISCUSSION

From the above analysis it is clear that a central core model of the renal medulla with active salt transport out of the thick AHL in the outer medulla and concentration by some combination of active transport and passive mixing of salt and urea in the inner medulla can qualitatively account for the known data of diuresis and antidiuresis. At the present time quantitative data are not available to determine the exact extent to which mixing induces a solute source out of the thin AHL and so generates the concentration profile of the inner medulla. As we have shown above, in theory the inner medulla could operate entirely passively. However, the theory also shows that any degree of urea cycling will depress core salt concentration relative to AHL salt concentration in both the inner and outer medulla and so reduce the local energy requirements for salt transport out of AHL, although overall, mixing dissipates free energy. The experimental data suggest that increased cycling plays an essential role in the transition of the kidney from diuresis to antidiuresis.

A detailed correlation of the theory with experimental data must account for several additional factors: in particular, the effect of reflection coefficients less than one, the effect of finite water and solute permeabilities, and the effect of imperfect vascular exchange. In general including these factors requires numerical solutions of the differential equations describing the system. The analytic theory presented in this and the preceding paper, however, gives intuitive insight into the operation of the system and is an indispensable guide to the detailed numerical analysis.

In conclusion, as with the single solute central core system, the most striking feature of the multisolute system is the continuous spectrum of its modes of operation. In theory the system can concentrate with almost any combination of solute cycling and water extraction and any combination of passive mixing and active transport. As we have shown above, however, application of the analytic model of the idealized central core system to the correlation of experimental data can set

definite constraints on the possible operating modes of the system. With further refinements of the theory and more extensive experimental data it should be possible to delimit more exactly the actual modes of operation of the medullary concentrating system.

APPENDIX

Introducing the change of variable $\xi = L - x$, we have from Eq. 41

$$c_{2M}(0)/c_{2M}(\xi) = e^{kg(\xi)}, \tag{A 1}$$

where

$$g(\xi) = \int_0^{\xi} [1 - \alpha(\xi)]\, d\xi \tag{A 2}$$

and

$$k = h_{24,s}/F_{1v}(L). \tag{A 3}$$

From Eq. 41 we have

$$A[\alpha(\xi)] = \frac{1 - f_V + f_V e^{kg(\xi)}}{1 + \dfrac{kh_u \displaystyle\int_0^{\xi} \alpha(\xi) e^{-kg(\xi)}\, d\xi}{h_s[1 - e^{-kg(\xi)}]}}, \tag{A 4}$$

where the right-hand side of Eq. A 4 is now regarded as an integral operator, which maps every integrable function $\alpha(\xi)$ into a function $A[\alpha(\xi)]$. Again we restrict the range of the functions to $0 \leq \alpha < 1$, and we have simplified notation by introducing h_u for $h_{34,u}$ and h_s for $h_{24,s}$. We seek the solution of Eq. A 4

$$A[\alpha(\xi)] = \alpha(\xi), \tag{A 5}$$

where

$$0 \leq \alpha(\xi) < 1. \tag{A 6}$$

We will designate this solution by $\alpha_F(\xi)$ and we will assume that it exists and is unique.

The iterative technique used to compute the solution depends on properties of the operator A for integrable functions satisfying condition A 6 which we will now prove.

THEOREM: If

$$\alpha(\xi) < \alpha'(\xi), \quad \text{for } \xi > 0, \tag{A 7}$$

then

$$A[\alpha(\xi)] > A[\alpha'(\xi)], \quad \text{for } \xi > 0, \tag{A 8}$$

and if

$$\alpha(\xi) > \alpha'(\xi), \quad \text{for } \xi > 0, \tag{A 9}$$

then

$$A[\alpha(\xi)] < A[\alpha'(\xi)], \quad \text{for } \xi > 0. \tag{A 10}$$

We shall prove only that relation (Re.) A 8 follows from Re. A 7; the proof of the second half of the theorem is similar. Let

$$\alpha'(\xi) = \alpha(\xi) + \epsilon(\xi), \tag{A 11}$$

where

$$\epsilon(\xi) > 0, \quad \text{for} \quad \xi > 0; \tag{A 12}$$

then we have

$$g'(\xi) = \int_0^\xi [1 - \alpha(\xi) - \epsilon(\xi)]\, d\xi, \tag{A 13}$$

or

$$g'(\xi) = g(\xi) - \Delta(\xi), \tag{A 14}$$

where

$$\Delta(\xi) > 0, \quad \text{for} \quad \xi > 0. \tag{A 15}$$

Substitution of Eqs. A 11 and A 14 into Eq. A 4 gives

$$A[\alpha'(\xi)] = \frac{(1 - f_v) + f_v e^{k[g(\xi) - \Delta(\xi)]}}{1 + \dfrac{h_u \displaystyle\int_0^\xi e^{-k[g(\xi) - \Delta(\xi)]}\, d\xi}{F_{1v}(L)[1 - e^{-k[g(\xi) - \Delta(\xi)]}]}}. \tag{A 16}$$

Eq. A 16 can also be written

$$A[\alpha'(\xi)] = \frac{(1 - f_v) + f_v e^{k[g(\xi) - \Delta(\xi)]}}{1 - \dfrac{h_u}{h_s} + \dfrac{kh_u \displaystyle\int_0^\xi e^{-k[g(\xi) - \Delta(\xi)]}\, d\xi}{h_s[1 - e^{-k[g(\xi) - \Delta(\xi)]}]}}. \tag{A 17}$$

From Eq. A 17 it can be seen that the effect of setting $\Delta(\xi) \equiv 0$ is to cause each term on the right-hand side to vary in such a way as to increase the right-hand side. Thus we have

$$A[\alpha'(\xi)] < \frac{1 - f_v + f_v e^{kg(\xi)}}{1 - \dfrac{h_u}{h_s} + \dfrac{kh_u \displaystyle\int_0^\xi e^{-kg(\xi)}\, d\xi}{h_s[1 - e^{-kg(\xi)}]}} \equiv A[\alpha(\xi)]. \tag{A 18}$$

Now let us suppose that we make an initial estimate $\alpha_0(\xi)$ with $\alpha_0(0) = \alpha_L$, where α_L is the solution of Eq. 44, and that the first iteration

$$\alpha_1(\xi) = A[\alpha_0(\xi)] < \alpha_0(\xi) \tag{A 19}$$

except for $\xi = 0$, where $\alpha_1(\xi) = \alpha_L$. We will further assume that $\alpha_F(\xi)$ is sufficiently well behaved that in some neighborhood $0 < \xi < b$, one of the three conditions

$$\alpha_F(\xi) > \alpha_0(\xi), \tag{A 20}$$

$$\alpha_0(\xi) \geq \alpha_F(\xi) \geq \alpha_1(\xi), \tag{A 21}$$

$$\alpha_1(\xi) > \alpha_F(\xi) \tag{A 22}$$

is satisfied. It immediately follows from the above theorem that only Re. A 21 is possible From Re. A 20 follows by the theorem

$$A[\alpha_F(\xi)] < A[\alpha_0(\xi)]. \tag{A 23}$$

Since $\alpha_F(\xi) = A[\alpha_F(\xi)]$, we have from Re. A 19 the contradiction of A 20

$$\alpha_F(\xi) < \alpha_1(\xi) < \alpha_0(\xi); \tag{A 24}$$

Re. A 22 is excluded by a similar argument leaving Re. A 21 as the only possibility. Thus $\alpha_F(\xi)$ lies between $\alpha_0(\xi)$ and $\alpha_1(\xi)$ until possibly it makes a first intersection with one of them. This cannot be with $\alpha_1(\xi)$ because then

$$\alpha_F(\xi) \leq \alpha_0(\xi), \tag{A 25}$$

which implies (since over a finite interval the inequality must be strict if the intersection occurs)

$$A[\alpha_F(\xi)] = \alpha_F(\xi) > A[\alpha_0(\xi)] = \alpha_1(\xi). \tag{A 26}$$

Thus if $\alpha_F(\xi)$ leaves the region between α_0 (ξ) and α_1 (ξ), its first intersection must be with $\alpha_0(\xi)$. This possibility is excluded if the condition

$$A[\alpha_1(\xi)] < \alpha_0(\xi), \xi > 0, \tag{A 27}$$

is satisfied, because then if $\alpha_F(\xi)$ intersects $\alpha_0(\xi)$ it must also intersect $A[\alpha_1(\xi)]$; but this is impossible because $\alpha_F(\xi) \geq \alpha_1(\xi)$ implies $A[\alpha_F(\xi)] = \alpha_F(\xi) \leq A[\alpha_1(\xi)]$.

Thus if we make an initial estimate $\alpha_0(\xi)$ and the iterates $A[\alpha_0(\xi)]$ and $A^2[\alpha_0(\xi)]$ satisfy the condition

$$\alpha_0(\xi) > A^2[\alpha_0(\xi)] > A[\alpha_0(\xi)], \xi > 0, \tag{A 28}$$

the solution $\alpha_F(\xi) = A[\alpha_F(\xi)]$ is bounded above by $\alpha_0(\xi)$ and below by $\alpha_1(\xi)$. It also lies between $A^2[\alpha_0(\xi)]$ and $A[\alpha_0(\xi)]$ because from Re. A 23 we have

$$A[\alpha_0(\xi)] < A^3[\alpha_0(\xi)] < A^2[\alpha_0(\xi)], \quad \xi > 0, \tag{A 29}$$

and the above argument can again be applied.

It should be noted that it always must be shown explicitly that Re. A 23 is satisfied. With the initial estimate used in the body of the paper the second iteration must be done by a numerical integration.

It should also be noted that if Re. A 23 is satisfied, that by repeated iteration we obtain the sequence

$$\alpha_0(\xi) > A^2[\alpha_0(\xi)] \ldots > A^{2n}[\alpha_0(\xi)] > A^{2n+1}[\alpha_0(\xi)] > \ldots A[\alpha_0(\xi)], \tag{A 30}$$

except for $\xi = 0$, where all the iterates equal α_L. Hence both the sequence of odd iterates $A^{2n+1}[\alpha_0(\xi)]$ and the sequence of even iterates $A^{2n}[\alpha_0(\xi)]$ converge to a limit. If these limits are identical, then the common limit must be $\alpha_F(\xi)$. So far we have been unable to establish analytical conditions for the identity of the limits, i.e., conditions for $\lim_{n\to\infty} | A^{2n}[\alpha_0(\xi)] - A^{2n+1}[\alpha_0(\xi)] | = 0$. Hence we have had to be satisfied with the weaker result of assuming the existence of $\alpha_F(\xi)$ and showing that it lies between successive odd and even iterates.

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