CONCENTRATION IN RENAL COUNTERFLOW SYSTEMS

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ABSTRACT In this paper earlier work on two-loop counterflow systems is extended to n-loop systems. It is shown that a large class of such systems in which exchange between the flow tubes is passive is unable to concentrate or dilute.

It is now a generally accepted hypothesis that production of urine hypertonic to plasma is effected by some type of renal counterflow system. The prototype of the mechanism is shown in Fig. 1. In this greatly simplified model nearly isotonic fluid from the proximal convoluted tubule enters the descending limb of Henle's loop. As this fluid travels down the limb it is concentrated either by extraction of water under a hydrostatic pressure difference between ascending and descending limbs or by active sodium transport into the descending limb. Either of these single effects, small for any given segment, multiplied down the length of the hairpin flow system will lead to a high sodium (i.e. solute) concentration at the tip of the loop (Hargitay and Kuhn, 1951). The final concentration of urine is obtained by extraction of water by the osmotic gradient from collecting duct fluid.

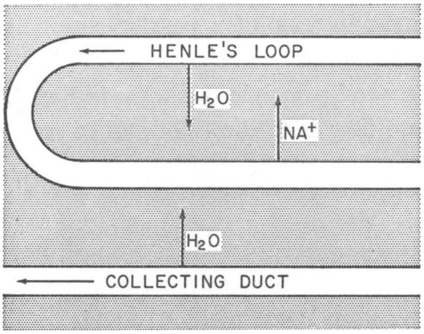

FIGURE 1 Prototype of countercurrent multiplier. Arrows indicate direction of sodium and/or water movement.

The details of the actual concentrating mechanism undoubtedly differ from either of these simple models (see Berliner, 1964, for a recent review of the physiological data) which both imply some physiological improbabilities. Among the complicating features is the parallel counterflow system in the vasa recta, the blood vessels supplying the renal medulla. It has been suggested (Pinter and Shohet, 1963) that the concentration profile in the renal medulla, known to increase to the very tip can be accounted for by active transport in only the thick portion of the ascending limb of Henle's loop, if exchange with the vasa recta is included in the analysis. In an earlier paper (Stephenson, 1965) it was shown by an analytical solution of the differential equations describing a two-loop system that the system suggested by Pinter and Shohet could not account for the concentration profile in the renal medulla. An analysis by Kelman and Marsh (1965) of the two-loop system reaches the same conclusion.

In this paper some qualitative ideas introduced in the earlier paper (Stephenson, 1965) are extended to the analysis of counterflow systems with any number of loops, and it is shown that a large class of such systems are unable to concentrate. The basic ideas used in the analysis are very simple. Namely, a function which is monotonic increasing, a function which is monotonic decreasing, and a function which is concave upward everywhere in a region; each will assume its maximum value at the boundary. Likewise under certain conditions the maximum envelope of families of such functions will assume its maximum value at the boundary. Detailed examination of the differential equations describing exchange in counterflow systems shows that at least some of the passive systems satisfy the necessary conditions; in these, the possibility of a maximum concentration in the interior of a passive region is excluded. A dual analysis applies to diluting systems.

The first system to which we will apply these general principles is shown in Fig. 2. There are n parallel flow tubes. In some of these flow is to the right and in some

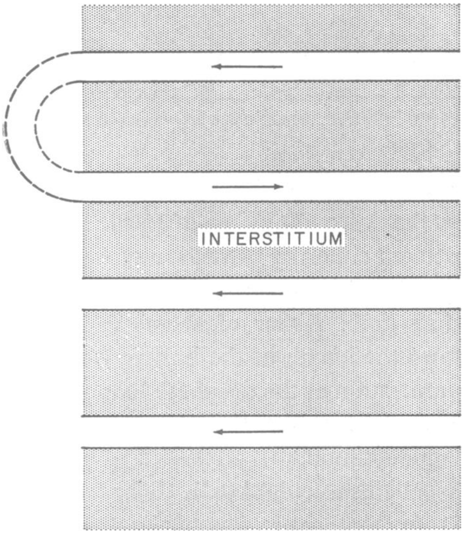

FIGURE 2 Parallel system of flow tubes free to exchange through interstitium. Some may have hairpin bend as indicated by dotted line.

flow is to the left. Also some tubes may be paired by a hairpin bend at the boundary. The aqueous solution in these tubes will be supposed to contain a single solute. This solute, but not the solvent, can exchange with solute in the surrounding interstitial medium (tubes do not directly exchange with one another). We will assume that longitudinal diffusion is negligible. Distance along the tubes, denoted by x, varies from 0 at the left-hand boundary to L at the right-hand boundary. Concentration in the ith tube is denoted by $c_i(x)$, concentration in the interstitium by $j(x)$, velocity of flow by $v_i(x)$, positive if flow is to the right, negative if flow is to the left. Since water does not exchange with the interstitium (in this model) $v_i(x)$ is constant for a given tube. Cross-sectional area of the tubes is assumed to be constant and to have value A_i so that transport of solute at point x, by the ith tube is $A_i v_i c_i(x)$. Permeability per unit length is h_i, also assumed to be constant, bounded, and positive, for a given tube and nondirectional. Thus for a segment of length dx, centered at x, of the ith tube, in which direction of (Fig. 3) flow is assumed to be to the right, influx by diffusion is $h_i\, j(x)\; dx$ and efflux is $h_i c_i(x)\; dx$. Influx by flow is $A_i v_i c_i(x - dx/2)$, and efflux is $A_i v_i c_i(x + dx/2)$. Subtracting efflux from influx yields the equation

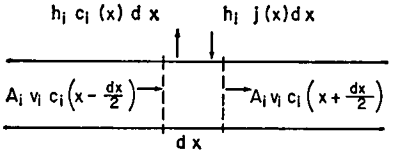

FIGURE 3 Flux of solute entering and leaving short segment of a single flow tube.

$$A_i v_i c_i(x - dx/2) + h_i j(x)\, dx - A_i v_i c_i(x + dx/2) - h_i c_i(x)\, dx = A_i\, dx \frac{\partial c_i(x)}{\partial t}. \tag{1}$$

As $dx \to 0$, this can be rearranged to yield

$$-v_i \frac{\partial c_i}{\partial x} = \frac{h_i}{A_i}(c_i - j) + \frac{\partial c_i}{\partial t} \tag{2}$$

In the steady state $\partial c_i/\partial t = 0$; also the A_i may be taken to have unit value without loss of generality. Thus we obtain for the ith tube the differential equation

$$-v_i \frac{dc_i}{dx} = h_i(c_i - j). \tag{3}$$

For the interstitial space (again with no longitudinal diffusion) we have the condition

$$\sum h_i(c_i - j) = 0 \tag{4}$$

or

$$j = \sum w_i c_i, \tag{5}$$

where $w_i = h_i/\Sigma h_i$. It follows that $\Sigma w_i = 1$ and $w_i > 0$. Equation (5) can be differentiated to give

$$\frac{dj}{dx} = \sum w_i \frac{dc_i}{dx}. \tag{6}$$

Careful note should be made of the fact that v_i is signed, positive for flow to the right, and negative for flow to the left. Note should also be made of the weighting factors w_i in equation (6) for dj/dx.

The boundary conditions also offer some practical difficulties. The solution of equations (3) and (5) is determined by the entering concentrations in the tubes and the condition that for tubes paired by a hairpin reversal of flow, concentrations match at the turnaround point. In general these are conditions set at both the right- and left-hand boundaries. Hence in solving the equations a complete set of $c_i(0)$ is assumed, some of which are actually fixed by the boundary conditions; the others are varied until the actual conditions are satisfied. More specifically, if j is eliminated from the system (3) by substitution from equation (5) we obtain the system

$$\frac{dc_i}{dx} = -\frac{h_i}{v_i}(1 - w_i)c_i + \sum_{k \neq i} \frac{h_i}{v_i} w_k c_k, \tag{7}$$

which can be written in matrix form

$$\frac{d\mathbf{c}}{dx} = \mathbf{A}\mathbf{c}, \tag{8}$$

where $\mathbf{c}$ is the column matrix with entries c_i, and $\mathbf{A}$ is an n by n matrix with entries $a_{ii} = -h_i(1 - w_i)/v_i$ and off-diagonal entries $a_{ik} = h_i w_k/v_i$.

Equation (8) has the well-known solution

$$\mathbf{c} = \mathbf{c}_0 e^{\mathbf{A}x} \tag{9}$$

(Gantmacher, 1959) where $\mathbf{c}_0$ is the column matrix with entries $c_i(0)$. The difficulty noted above is that all of the $c_i(0)$ are not directly specified, but must be obtained from the subsidiary equations

$$\mathbf{c}(L) = \mathbf{c}_0 e^{\mathbf{A}L}, \tag{10}$$

where some of the $c_i(L)$ are specified, and

$$c_i(0) = c_{i+1}(0), \tag{11}$$

where i and $i+1$ denote tubes paired by a hairpin bend. If we want to consider bends at the right-hand boundary as well, we will have additional conditions

$$c_i(L) = c_{i+1}(L). \tag{12}$$

In any event, for a solution, equations (10), (11), and (12) together with the specified $c_i(0)$ must lead to a system of linear algebraic equations which can be solved for a unique set of $c_i(0)$.

The actual solution of the system (8) need not concern us further except to note that the $c_i(x)$ and $j(x)$ are analytic functions of x, and so have a Taylor's series expansion.

We next consider the maximal envelope of the various concentrations in the region 0 to L. This we define by

$$c_{\max}(x) = \max_i \, [c_i(x), j(x)]. \tag{13}$$

We also define a minimal envelope by

$$c_{\min}(x) = \min_i \, [c_i(x), j(x)]. \tag{14}$$

Thus $c_{\max}(x)$ is constructed from a family of intersecting arcs from the various $c_i(x)$ and $j(x)$.

If at any point, for all i, we have $c_i = j$, then from equations (3) and (5) we have the trivial solution

$$c_i = j = c_{\max} = c_{\min} = \text{constant}, \qquad 0 \leq x \leq L. \tag{15}$$

Apart from this case, because j is the weighted mean of the c_i, we have

$$c_{\max}(x) > j(x) > c_{\min}(x). \tag{16}$$

That is, unless the concentrations throughout the region are equal and constant, the interstitial concentration j will be bracketed above and below by some of the c_i. We will now show that the c_i are majorized by one of the entering concentrations.

For flow in the positive x direction, that is to the right, we see from equation (3) that $dc_i/dx < 0$, if $c_i > j$, and that $dc_i/dx > 0$ if $c_i < j$. Conversely for flow to the left $dc_i/dx < 0$ if $c_i < j$ and $dc_i/dx > 0$ if $c_i > j$. Stated in another way, for a given tube dc_i/dx can change sign only if c_i intersects j. This excludes a local extreme value for any arc of the maximum envelope belonging to a particular c_i. The maximal envelope c_i will be constructed from a set of intersecting monotone decreasing and monotone increasing arcs. An interior maximum could occur only on a transition from a monotone increasing arc on the left to a monotone decreasing on the right (Fig. 4). Such a transition is forbidden because it would violate the assumption we were on the maximal envelope to the right and left of the transition point. This is intuitively obvious from the extrapolated dotted lines in Fig. 4. A rigorous argument follows. Let us designate the monotone increasing arc on the left by c_j and the monotone decreasing on the right by c_k, the intersection point by x_t. We can develop c_j and c_k in a Taylor's series about x_t, yielding

$$\begin{aligned} c_j &= c_j(x_t) + \left[\frac{dc_j}{dx}\right]_{x_t}(x - x_t) + \left[\frac{d^2c_j}{dx^2}\right]_{x_t}\frac{(x - x_t)^2}{2!} + \cdots \\ c_k &= c_k(x_t) + \left[\frac{dc_k}{dx}\right]_{x_t}(x - x_t) + \left[\frac{d^2c_k}{dx^2}\right]_{x_t}\frac{(x - x_t)^2}{2!} + \cdots \end{aligned} \tag{17}$$

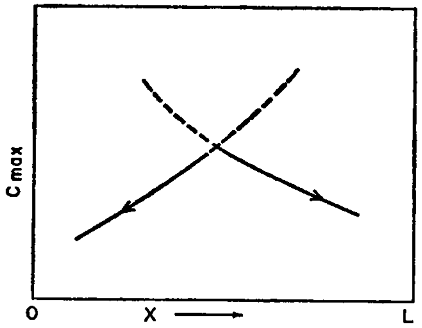

FIGURE 4 Forbidden transition on the maximal envelope. Arrows indicate direction of flow in tubes contributing arcs to the envelopes. As discussed in the text, two curves, called the maximal and minimal envelopes, will bound all interior concentrations in the system. These curves are constructed from segments of concentration curves belonging to the various flow tubes. Interior maxima might occur (*a*) on a segment belonging to a single flow tube or (*b*) on a transition from segments belonging to different tubes. Both types can be excluded by arguments based on the differential equations describing the system. A dual argument applies to interior minima.

Substracting c_k from c_j, we obtain

$$c_j - c_k = c_j(x_t) - c_k(x_t) + \left[\left[\frac{dc_j}{dx}\right]_{x_t} - \left[\frac{dc_k}{dx}\right]_{x_t}\right](x - x_t) + \left[\left[\frac{d^2c_j}{dx^2}\right]_{x_t} - \left[\frac{d^2c_k}{dx^2}\right]_{x_t}\right]\frac{(x - x_t)^2}{2!} + \cdots \tag{18}$$

By hypothesis $[dc_j/dx]_{x_t} > 0$ and $[dc_k/dx]_{x_t} < 0$ and $c_j(x_t) = c_k(x_t)$, also the second and all higher coefficients are bounded say by $B > 0$. The problem is to prove that for some value of $x - x_t$ in the right-hand neighborhood of x_t, $c_j - c_k > 0$. By hypothesis we have

$$A = \left[\left[\frac{dc_j}{dx}\right]_{x_t} - \left[\frac{dc_k}{dx}\right]_{x_t}\right] > 0,$$

and if all higher coefficients are replaced by their upper bound B,

$$c_j - c_k \geq A(x - x_t) - B[(x - x_t)^2 + (x - x_t)^3 + \cdots] \tag{19}$$

Summing the bracketed geometric series in expression (19) we obtain

$$\begin{aligned} c_j - c_k &\geq A(x - x_t) - B(x - x_t)^2 \frac{1}{1 - (x - x_t)} \\ &\geq A(x - x_t)\left[1 - \frac{B}{A}\frac{(x - x_t)}{1 - (x - x_t)}\right] \\ &\geq 0 \quad \text{for} \quad 0 \leq x - x_t \leq \frac{1}{1 + \dfrac{B}{A}} \end{aligned} \tag{20}$$

If we set

$$x - x_t = \frac{1 - \alpha}{\frac{B}{A} + 1 - \alpha} \tag{21}$$

where $0 < \alpha < 1$ we have

$$c_i - c_k \geq A\alpha\left[\frac{1 - \alpha}{\frac{B}{A} + 1 - \alpha}\right] > 0$$

Or for this value of $x - x_t$, $c_j > c_k$. This contradicts the hypothesis that this arc of c_k is part of the maximal envelope. Thus the assumed transition is forbidden.

Therefore as the maximal envelope is traced from left to right it may be composed of a set of monotone decreasing arcs, a set of monotone increasing arcs, or a set of monotone decreasing on the left and monotone increasing on the right, with a single transition from monotone decreasing to monotone increasing. These three possibilities are illusrtated in Fig. 5. As we have noted the decreasing arcs are from tubes in which flow is to the right and the increasing from tubes in which flow is to the left. Thus in all cases the upper bound of the maximal envelope will occur at 0 or L and will belong to a tube in which flow is *into* the region at 0 or L. A similar argument applies to the minimal envelope, and leads to the possibilities shown in Fig. 6. If

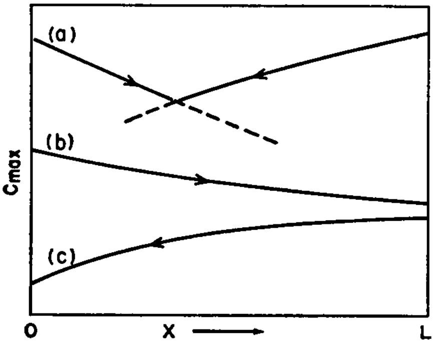

FIGURE 5 Possible types of maximal envelope after the exclusion of interior maxima: (*a*) single transition from monotone decreasing to monotone increasing, (*b*) monotone decreasing, (*c*) monotone increasing. In each type the concentration in some entering flow is greater than all interior concentrations.

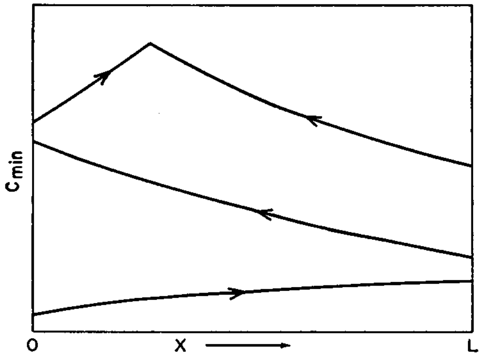

FIGURE 6 Types of minimal envelope. A dual argument shows that the concentration of some entering flow is less than all interior concentrations.

all of the tubes enter at the right but some make a hairpin bend at the left-hand boundary, each of those which turns and for which $c_i > j$ will supply an increasing and decreasing function which are equal at the left-hand boundary (Fig. 7). Those tubes with a hairpin bend for which $c_i < j$ will also supply increasing and decreasing functions but with reversal of flow (Fig. 7). Thus we will have envelopes of the form shown in Fig. 8 when all tubes enter from the right either to flow through the system or to make a hairpin bend at the left-hand boundary. Hence in this type of system the interior concentrations, including the interstitial concentration, are both majorized and minorized by one of the entering concentrations. That is, all of the interior concentrations lie between the maximum and minimum entering concentrations.

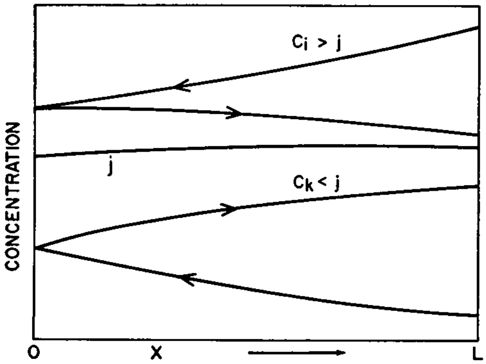

FIGURE 7 Types of concentration profile in tube with hairpin bend. Direction of flow indicated by arrows. Note reversal of slope for same direction of flow for concentrations larger and smaller than interstitial concentrations.

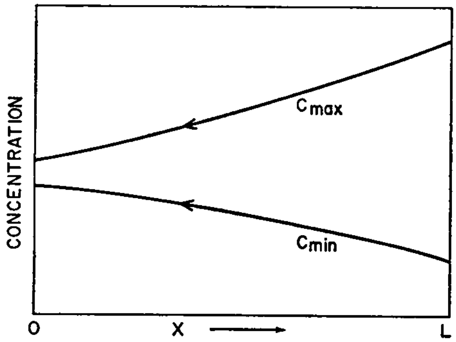

FIGURE 8 Maximal and minimal envelopes when all tubes enter from the right including those with hairpin bends at the extreme left.

It is clear that since the interior concentrations in a system described by the equations (7) cannot exceed the maximum entering concentration such a system is not a concentrating system in the usual sense. A possible source of confusion in the interpretation of solutions of the differential equations is that the interstitial concentration can either increase or decrease to the left, that is, physiologically speaking, toward the inner medulla.

In a counterflow system which concentrates by active transport or hydrostatic filtration one or more of the concentrations can, of course, rise markedly above the maximum entering concentration. We will suppose that such a system is to the right of the passive system we have discussed above and extends from L to L_1.

We will suppose all tubes enter at the right. In this region we will suppose that concentration occurs by active transport from one or more of the ascending limbs (i.e. tubes in which flow is to the right into the interstitial space). In the region (L, L_1) the equation for these tubes becomes

$$v_i \frac{dc_i}{dx} = -h_{ki}c_i + h_{ik}j \tag{22}$$

where the doubly subscripted h_{ki} is the transport coefficient from the tube to the interstitium and h_{ik} is the transport coefficient from the interstitium to the tube; v_i, h_{ki}, and h_{ik} are all positive. For active transport from the tube $h_{ki} > h_{ik}$. To simplify the analysis we will suppose that in those tubes with active transport $h_{ik} = 0$. (That is, solute can be transported out of these ascending limbs but cannot diffuse back in.) For those tubes in which transport is passive we have $h_{ki} = h_{ik} = h_i$, where h_i is the permeability in the passive region. For the interstitial concentration we have the new equation

$$\sum_i - h_{ki}c_i + \sum_i h_{ik}j = 0 \tag{23}$$

or

$$j = \sum h_{ki}c_i / \sum h_{ik}. \tag{24}$$

Since $h_{ik} = h_i$ for tubes in which transport is passive and is 0 otherwise, it follows that in the active region Σh_{ik} is less than Σh_i in the passive region. Thus,

$$j = \sum w_i' c_i, \tag{25}$$

where in tubes with passive transfer

$$w_i' > w_i. \tag{26}$$

In the tubes with active transfer the relative magnitude of the weighting factors w_i' and w_i will depend on the value of h_{ki}, but in general they will not be equal. If one assumes that $h_{ki} = h_i$, then expression (26) will hold. This discontinuity in the weighting factors in the equation for interstitial concentration, together with the assumption that all concentrations in the tubes, c_i, are continuous at L, usually results in a jump discontinuity of j at L with

$$j(L - 0) < j(L + 0). \tag{27}$$

If longitudinal diffusion were allowed in our model, this discontinuity would disappear.

If we assume that all concentrations in tubes entering the system at the extreme right, L_1, are no greater than c_p (that is physiologically speaking no greater than the plasma concentration) and that $c_{\max}(L) > c_p$ (certainly a necessary criterion for a concentrating system), we can show that $c_{\max}(L)$ is majorized by some value of the interstitial concentration to the right of L. The argument follows:

If $j(L+0) > c_{\max}(L)$ there is nothing to prove. If $j(L+0) < c_{\max}(L)$, since we have shown that in a system in which all tubes enter at the right (see Fig. 8), $c_{\max}(L)$ occurs in one of the tubes in which flow is to the left (i.e. descending), we have $dc_{\max}(L)/dx > 0$. By hypothesis $c_{\max}(L_1) = c_p$ and $c_{\max}(L) > c_p$. Consequently at some point β, $L \leq \beta \leq L_1$, $dc_{\max}/dx$ must change sign, because if it remained positive c_{max} would have to increase to the right and one would have $c_p = c_{\max}(L_1) > c_{\max}(L)$, a contradiction. At this point $c_{\max}(\beta) = j(\beta) > c_{\max}(L)$.

Therefore $j(\beta)$ maximizes all concentrations in the passive region to the left of L, since $c_{\max}(L)$ is greater than any of these.

The above system is particularly artificial in that longitudinal diffusion is not permitted. However, the analysis is easily extended to include longitudinal diffusion in the interstitium. In this case solute can enter or leave a volume element of the interstitium not only via one of the flow tubes, but also by diffusion. The net rate of accumulation by diffusion is $D(\partial^2 j/\partial x^2)$, where D is the diffusion coefficient. In the steady state the differential equation for the interstitial concentration is

$$D\frac{d^2 j}{dx^2} = -\sum h_i(c_i - j). \tag{28}$$

The other equations remain the same; i.e.,

$$-v_i\frac{dc_i}{dx} = h_i(c_i - j). \tag{29}$$

If some $c_i > j$ the argument of the previous case remains the same, and the maximal envelope is constructed from arcs of the various $c_i > j$. Local interior maxima are excluded by the identical arguments used earlier. If all $c_i \leq j$ and at least one $c_i < j$ then $d^2j/dx^2 > 0$. Then this portion of the maximal envelope is constructed from j and is concave upward. All that remains is to show that an interior maximum is excluded on a transition from a portion of the maximal envelope constructed from j to a portion constructed from one of the c_i. A transition of the type indicated in Fig. 9 where to the left $j > c_i$ and to the right some $c_i > j$ and at the transition point α, $dj/dx > 0$ and $dc_i/dx < 0$ is forbidden. Both the intuitive and rigorous arguments are identical with those given earlier. There remains a transition such that at the transition point, α, $dj/dx = 0$ and $d^2j/dx^2 = 0$. The second condition together with $j \geq c_i$ for all i implies that $j = c_i$ for all i. Thus the first and all higher derivatives of j and all c_i vanish at the point α. Therefore, we have all concentrations constant throughout the region.

The analysis can also be extended to include transtubular movement of water.

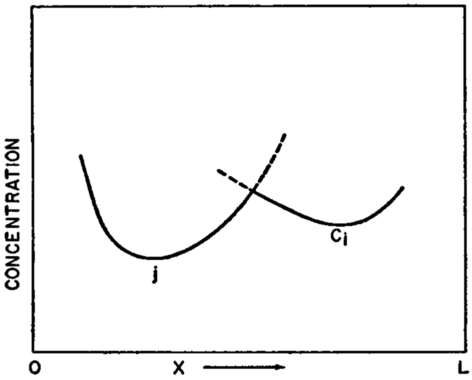

FIGURE 9 Maximal envelope constructed from arcs of j and c_i with longitudinal diffusion in the interstitium. Transition illustrated is forbidden.

If we exclude longitudinal diffusion in the tubes and bulk flow in the interstitium we have the equations:

$$\frac{d(v_ic_i)}{dx} = -h_i(c_i - j), \tag{30}$$

and

$$\frac{dv_i}{dx} = p_i(c_i - j), \tag{31}$$

with the additional condition

$$\sum p_i(c_i - j) = 0 \tag{32}$$

where p_i is the water permeability. For equation (32) we see that again the interstitial concentration is the weighted mean of the various tubal concentrations. From equations (30) and (31) we obtain

$$\frac{d(v_ic_i)}{dx} = -\alpha_i \frac{dv_i}{dx} \tag{33}$$

where α_i has been substituted for the ratio of the permeabilities h_i/p_i. Upon integrating equation (33) we obtain

$$v_i(c_i + \alpha_i) = K_i \tag{34}$$

where K_i is a constant of integration. Since $(c_i + \alpha_i)$ is positive, equation (34) shows that K_i is positive for flow to the right and negative for flow to the left; it also shows that for a given tube v_i retains its sign.

Differentiation of equation (30) yields

$$v_i \frac{dc_i}{dx} + c_i \frac{dv_i}{dx} = -h_i(c_i - j), \tag{35}$$

which on substitution from equations (34) and (31) becomes

$$\frac{dc_i}{dx} = -\frac{(c_i + \alpha_i)}{K_i}(h_i + c_ip_i)(c_i - j) \tag{36}$$

The factor $(c_i + \alpha_i)(h_i + c_i p_i)/K_i$ is positive for flow to the right and negative for flow to the left. The previous argument, for the case of no transtubular movement by water, involves only the sign of dc_i/dx relative to $(c_i - j)$ and so carries through when transtubular movement of water is allowed without modification to the same conclusion: all interior concentrations must lie between the maximum and minimum entering concentrations.

The systems discussed above have been shown to be untenable as concentrating mechanisms on the basis that the differential equations describing them are such that all interior concentrations and hence the concentrations of all outflows must lie between the maximum and minimum entering concentrations. It seems likely that the type of analysis used in this paper can be extended to exclude other types of systems are concentrating devices. One must be careful, however, in the generality of his extrapolations from this analysis. The systems which have been analyzed do not include hydrostatic pressure and pressure flow relations and only consider a single solute. In the type of model considered, certainly a sodium pump restricted to the outer medulla cannot account for the sodium concentration in the inner medulla. This is not to say that a sodium pump in the outer medulla could not conceivably produce a hydrostatic pressure which was used to drive a countercurrent multiplier in the inner medulla. Such a modified model would have to be accepted or rejected on its own merits.

The limitations of general thermodynamic arguments applied to this type of system should also be specifically noted. If an otherwise isolated system has a single inflow of solution of salt and water at a given osmolality and in the interior of the system some combination of processes takes place so that this inflow is separated into two outflows of different osmolalities, work must be done on the system. Otherwise one would have an isolated system in which the entropy was spontaneously decreasing, in violation of the second law of thermodynamics. If, however, there are two or more inflows at different osmolalities, there is no theoretical reason why these cannot be coupled to an osmotic "engine"; e.g., a cylinder in which the piston is suitably semipermeable, and used to perform useful work. This work could then be used to concentrate another part of the inflow and eventually yield some fraction of the outflow at higher concentration than any part of the inflow. But regardless of the details, if a system has efflux of solution at greater osmolality than any influx there must be some process in the system whose over-all effect is to transport solute from a region of lower to one of higher concentration or to move solvent from a region of higher to one of lower solute concentration. Either of these processes require the performance of work at the *site of transport.*

None of the systems discussed above and discarded on the basis of purely mathematical arguments have any provision for performing useful work of concentration. The processes going on in them are purely dissipative: diffusion of sodium along a concentration gradient, passive transfer of sodium across a membrane, transport of water with no pressure differential. Again one should keep an open mind; it is conceivable that the inner medulla could employ some undiscovered mechanism for carrying out the work of concentration, but regardless of the mathematical obfuscation of a model it must have some way of doing this necessary work.

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