CONCENTRATING ENGINES AND THE KIDNEY

I. CENTRAL CORE MODEL OF THE RENAL MEDULLA

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ABSTRACT Mass balance relations, valid for any counterflow system, are derived and applied to a central core model of the renal medulla, in which descending Henle's limbs (DHL), ascending Henle's limbs (AHL), and collecting ducts (CD) exchange with a central vascular core (VC) formed by vasa recta loops, assumed so highly permeable that the core functions as a single tube open at the cortical end, closed at the papillary. Solute supplied to the VC primarily by the water impermeable AHL may either enter the DHL to be recycled or remain in the core to extract water by osmosis from DHL and CD. If concentrations in core and descending flows are nearly equal, then for all degrees of recycling the ratio of entering DHL concentration to loop concentration is given by $r = 1/[1 - f_T(1 - f_U)]$, where f_T is the fractional net solute transport out of AHL and f_U is the ratio of CD flow to the sum of CD and AHL flows. Differential equations for a single solute are derived for core and AHL concentrations. Explicit analytic solutions are given for solute transport out of the AHL governed by Michaelis-Menten kinetics. Finally the energy requirements for concentration are analyzed.

INTRODUCTION

In this paper we begin the analysis of continuous flow concentrating engines and their relation to the formation of urine by the mammalian kidney. These engines all utilize continuous counterflow and active solute transport to separate homogenous inflowing solutions into nonidentical outflowing fractions. Thus, chemical energy is used to increase the free energy of the inflowing solution. Because of rapidly advancing membrane technology and a variety of engineering problems such as desalinization and fractionation of waste effluents, the analysis of these engines is interesting in its own right. Our interest, however, is centered on the problem of urine formation from glomerular filtrate.

Historically, the consideration of such engines arose from the problem of how mammals and birds can produce a urine more concentrated than blood plasma and glomerular filtrate. In mammals this ability varies between species, being most marked in desert rodents, some of which, such as the golden hamster and *Psammomys*, can produce urines of concentrations greater than 4,000 mosmol/liter, corresponding to a van't Hoff osmotic pressure of nearly 100 atm. It had been noted by several investigators (see Dicker, 1970, for a summary of the early literature) that this ability to concentrate urine was correlated with the possession of Henle's loop, but the mechanism of concentration was not understood at all until 1942, when Kuhn and Ryffel (1942) suggested that the loop provided a countercurrent system in which a small single effect could be multiplied many-fold. This hypothesis, elaborated by Kuhn and his co-workers in a series of papers, has gradually become accepted in general, although the details are disputed.

The hypothesis in one of its original variants is illustrated in Fig. 1. As fluid flows down the descending limb of Henle's loop it is concentrated either by the entry of salt or by the extraction of water (or both), and as it flows up the ascending limb it is correspondingly diluted by removal of salt or entry of water. Theoretically, the driving force could be either a hydrostatic pressure difference between ascending and descending limbs, as originally suggested by Hargitay and Kuhn (1951), or active salt transport from ascending to descending limb as subsequently suggested (Wirz et al., 1951; Kuhn and Ramel, 1959 *a*, *b*); but since the hydrostatic pressure difference between ascending and descending limbs is only a few millimeters of Hg, active salt transport is the only likely possibility. Final concentration of urine is obtained by transfer of water from CD to loop structures as CD fluid traverses the osmotic gradient maintained by the multiplication process.

Although such a system, with mass transfer restricted to tubular structures, would work in principle, micropuncture studies (see Gottschalk, 1964, for a review of the early micropuncture literature, and Marsh, 1971, for a comprehensive recent review) indicate that water and salt are both removed from the loop structures, as well as water and probably salt from the CD. Thus, there is net entry of both salt and water into the medullary interstitium. This water and salt must be taken up by the capillaries, because there are no medullary lymphatics (Kriz, 1970) and bulk interstitial flow seems highy improbable. In the steady state, capillary uptake must

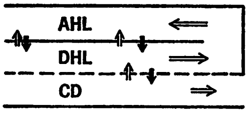

FIGURE 1

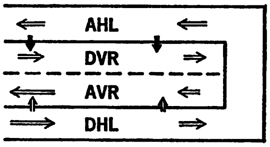

FIGURE 2

FIGURE 1 One variant of Kuhn and Ramel's countercurrent multiplier. Water moves from descending limb of Henle's loop (DHL) to ascending (AHL) or solute from AHL to DHL. Water and solute move between DHL and collecting duct (CD), so CD and DHL attain nearly the same osmolality. ⇒, water movement; ➔, solute movement.

FIGURE 2 Central core system, visualized as formed by the folding of two parallel tubes on the tube corresponding to the vasa recta. Dashed line indicates opposing walls of ascending vasa recta (AVR) and descending vasa recta (DVR).

balance entry from the renal tubules. Otherwise, water accumulation would raise the interstitial hydrostatic pressure and completely shut down renal function. The capillaries also form a highly efficient countercurrent exchange system which has been recognized as essential in preventing the washout of the medullary concentration gradient (Wirz, 1956; Berliner et al., 1958; Ullrich et al., 1962). Clearly, any realistic model of the medullary concentrating system must incorporate the vasa recta and account for the movement of both solutes and water. Attempts to satisfy these requirements have met with difficulties. Analytical solutions (Stephenson, 1965, 1966; Kelman et al., 1966) have been restricted to models that permit only solute movement. Computer simulations (Jacquez et al., 1967; Kien and Koushanpour, 1968) have also had limited success in accounting for both water and solute movement. One difficulty is that a large class of models in which tubules and vasa recta exchange with a well-mixed interstitium is inconsistent (Stephenson, 1971).

In the attempt to develop consistent models which incorporate the vasa recta and include water and solute movement we have been led to the class of concentrating engines whose prototype is illustrated in Figs. 2–4. Solute is pumped into a central core, blind at one end, open at the other, from a flow tube corresponding to AHL. Solution in the tubes corresponding to DHL and CD is concentrated primarily by water extraction. These engines utilize a fundamentally different topological connectivity than the engine of Fig. 1. The system can be visualized as arising from the folding of two parallel flow tubes, one corresponding to the renal tubule and the other to the vasa recta, then obliterating the internal folded capillary wall. This idealizes the exchange function of the capillaries so that washout is entirely due to water taken up by the vascular core from the tubule. Transport of solute

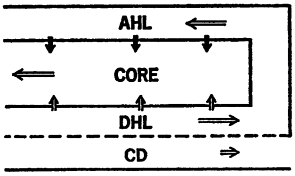

FIGURE 3

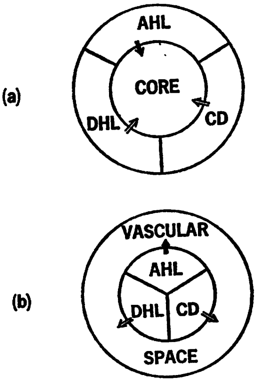

FIGURE 4

FIGURE 3 Central core system showing vasa recta merged to form a single tube, closed at the loop end, open at the other. In this plane view, CD is shown as merged with the DHL.
FIGURE 4 (*a*) Cross-section of central core model showing AHL, DHL, and CD grouped around core. (*b*) Shows a peripheral vascular space. Both configurations have the essential property that AHL, DHL, CD, and vascular space are in mutual contact.

and water, however, is from the tubule to the folded vascular core; i.e. from the *inside* of the tubule to the *outside* as it is in the proximal and distal convoluted tubule, with the difference that solute is supplied from AHL and water from DHL instead of both from the same segment of tubule. Some recycling of solute from AHL to DHL may occur, but analysis shows that with no recycling the engine attains a given concentration ratio between entering and loop fluid with minimum solute transport. This engine splits the entering solution into three fractions. In contrast, in the engine of Fig. 1, transport of solute and water is from the *inside* of the tubule to the *inside* of the tubule across the folded membrane separating AHL and DHL, and entering solution is split into two fractions.

It is our hypothesis that the highly organized anatomical units described by Kriz and others constitute functional *nephrovascular units* whose general mode of operation parallels that of the central core concentrating engine (CCE) and whose idealized operation is analogous to that of a CCE in exactly the same way as the operation of an internal combustion engine is analogous to an ideal engine utilizing an Otto cycle. We are thus able to construct an approximate analytical theory of urine formation which incorporates salt, water, and urea movement between tubules and capillaries.

In this paper we analyze the behavior of a central core engine, restricting the the theory to transport of a single solute and water under highly idealized conditions. In the following paper, we extend the analysis to multisolute systems. Later papers will extend the theory to less idealized systems and apply it to the detailed analysis of experimental data. Preliminary accounts of the model have been given elsewhere (Stephenson, 1972, 1973).

MASS BALANCE EQUATIONS

In this section, repeatedly used mass balance relations for solute and water transport are derived from flow equations for a mutually exchanging set of parallel tubes. These flow tubes exchange directly with one another through common-bounding surfaces (membranes) and not indirectly via a well-mixed interstitial compartment.[1] If we denote the length of the boundary between transverse sections of the ith and jth tubes by B_{ij} and the net outward flux per unit area of the kth substance from the ith to the jth tube by $J_{aij,k}$, then the total net outward transport of the kth substance through the surface element B_{ij} dx is $J_{aij,k}B_{ij}$ dx $= J_{ij,k}$. The net outward flux of the kth substance from the ith tube per unit length is $J_{ik} = \sum_j J_{ij,k}$. If then, F_{ik} is the total axial flux of the substance, A_i the cross-sectional area, and

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[1] The connectivity of such a system for any given transverse section is, of course, limited. Not more than four plane areas can be neighboring domains, i.e., possess a common boundary of *finite* length (Tietze, 1965). Thus, no more than four tubes can be in mutual contact along their entire length. Three-dimensional braiding and anastomosis can increase the number of mutually exchanging tubes, but systems using four mutually connected flow tubes that are discussed in this paper are more general than might appear at first.

s_{ik} the average net rate at which material is being produced or destroyed within the tube by chemical or physical reaction, the equation for mass continuity is:

$$(-\partial F_{ik}/\partial x) + A_i s_{ik} - J_{ik} = \partial(A_i c_{ik})/\partial t, \tag{1}$$

where c_{ik} is the concentration of the kth solute in the ith tube. In the steady state with $s_{ik} = 0$, Eq. 1 reduces to

$$\mathrm{d}F_{ik}/\mathrm{d}x = -J_{ik}. \tag{2}$$

A similar equation holds for total mass flow. Thus,

$$\mathrm{d}F_{iM}/\mathrm{d}x = -J_{iM}, \tag{3}$$

where $F_{iM} = \sum_k F_{ik}$ and $J_{iM} = \sum_k J_{ik}$. Likewise for an incompressible fluid the equation for total volume flow is

$$\mathrm{d}F_{iv}/\mathrm{d}x = -J_{iv}. \tag{4}$$

For dilute aqueous solutions, total mass and volume flow equal approximately the mass and volume flow of water. Integration of Eq. 2 gives

$$F_{ik}(x_1) - F_{ik}(x_2) = \int_{x_1}^{x_2} J_{ik}\,\mathrm{d}x, \tag{5}$$

and by the mean value theorem,

$$F_{ik}(x_1) - F_{ik}(x_2) = \hat{J}_{ik}[x_2 - x_1] \tag{6}$$

Eq. 6 and the corresponding integral forms of Eqs. 3 and 4 will be used constantly with the assumption that there is a constant outward transport J_{ik} along the tube equal to the mean transport $\hat{J}_{ik}$. For results which depend only on total transport out of the tube, it is convenient to introduce the transport integrals,

$$T_{ik}(x) = \int_0^x J_{ik}(x)\,\mathrm{d}x. \tag{7}$$

Then

$$F_{ik}(x_1) - F_{ik}(x_2) = T_{ik}(x_2) - T_{ik}(x_1). \tag{8}$$

Used without an argument, T_{ik} is the total net transport of the kth solute out of the ith tube, i.e.,

$$T_{ik} = \int_0^L J_{ik}\,\mathrm{d}x = \hat{J}_{ik}L, \tag{9}$$

where L is the total length of the flow tube.

We assume that the radial concentration gradient is negligible and that the total axial flux is given by

$$F_{ik} = F_{iv}c_{ik} - A_i D_{ik}(\mathrm{d}c_{ik}/\mathrm{d}x), \tag{10}$$

where D_{ik} is the diffusion coefficient of the kth solute in the ith tube (not necessarily the self-diffusion coefficient of the kth solute in dilute aqueous solution). Substitution of Eq. 10 into Eq. 2 gives

$$(\mathrm{d}/\mathrm{d}x)[-A_i D_{ik}(\mathrm{d}c_{ik}/\mathrm{d}x) + F_{iv}c_{ik}] = -J_{ik}. \tag{11}$$

If we set $A_i = 1$, assume D_{ik} is nearly constant, and carry out the differentiation, we obtain,

$$-D_{ik}(\mathrm{d}^2c_{ik}/\mathrm{d}x^2) + (\mathrm{d}F_{iv}/\mathrm{d}x)c_{ik} + F_{iv}(\mathrm{d}c_{ik}/\mathrm{d}x) = -J_{ik}. \tag{12}$$

From Eqs. 12 and 4 we derive

$$-D_{ik}(\mathrm{d}^2c_{ik}/\mathrm{d}x^2) + F_{iv}(\mathrm{d}c_{ik}/\mathrm{d}x) = -J_{ik} + J_{iv}c_{ik}. \tag{13}$$

If the diffusional term is small relative to the bulk flow term, Eq. 13 reduces to

$$\mathrm{d}c_{ik}/\mathrm{d}x = (-J_{ik} + J_{iv}c_{ik})/F_{iv}, \tag{14}$$

at points where $F_{iv} \neq 0$. If $F_{iv} > 0$, $\mathrm{d}c_{ik}/\mathrm{d}x$ has the sign of $-J_{ik} + J_{iv}c_{ik}$. Thus, $\mathrm{d}c_{ik}/\mathrm{d}x > 0$ if $c_{ik} > J_{ik}/J_{iv}$, an intuitively obvious relation if one notes that J_{ik}/J_{iv} is the concentration of the kth solute in the net transmural transport out of the ith tube. If the diffusional term is retained, this conclusion no longer holds.

In the absence of transitions of one species to another in the membranes separating the tubes, the flux from i to j is equal and opposite to the flux from j to i, or

$$J_{ij,k} = -J_{ji,k}, \tag{15}$$

from which we derive

$$\textstyle\sum_i J_{ik} = 0. \tag{16}$$

Summation of Eqs. 2 over i, and utilization of Eqs. 15 gives the integrated relations

$$\textstyle\sum_i F_{ik}(x) = \sum_i F_{ik}(0) = \sum_i F_{ik}(L). \tag{17}$$

A similar derivation gives

$$\textstyle\sum_i F_{iv}(x) = \sum_i F_{iv}(0) = \sum_i F_{iv}(L). \tag{18}$$

It should be emphasized that the above relations are all *mass balance* relations and introduce no assumptions whatsoever about driving forces causing the transport. Specifically, $J_{iv}c_{ik}$ in Eq. 14 is not a "drag" term.

The mathematical description of the system is completed by an equation of motion for the fluid in the *i*th tube

$$dP_i/dx = -R_{iF}(x)F_{iv}(x), \qquad (19)$$

where P_i is the hydrostatic pressure, and R_{iF} is the flow resistance of the tube; and by the laws relating the fluxes $J_{ij,k}$ and $J_{ij,v}$ to the pressures and concentrations in the *i*th and *j*th tubes.

Many of the results in this paper are independent of the particular transport mechanisms assumed for the fluxes. Particular laws for the *J*'s are introduced as required in the theoretical development. In the central core model the kidney's composite membrane systems, e.g. DHL wall, interstitial space, ascending vasa recta wall, are approximated by single membranes separating the flow tubes. In the first-order theory of this and the following paper, on the basis of the available experimental data (see Marsh, 1971), hydrostatic pressure is assumed to be a negligible driving force across these single approximating membranes, and the equations of motion are not used.

CENTRAL CORE OSMOTIC ENGINES

The central core engine can utilize as a single effect solute cycling from ascending to descending flow, osmotic water extraction from the descending flow, or a combination of the two. With pure solute cycling the central core essentially becomes nonfunctional, serving only as a conduit for the transverse exchange of solutes and water. The operation of the water-extracting engine can be most easily understood from the reduced system consisting of central core and one descending flow tube. If in a static two compartment system (Fig. 5) in which the compartments are separated by a water permeable, solute impermeable membrane, solute is added to one compartment; the concentration in this compartment will be increased and water will be osmotically withdrawn from the other compartment until equilibrium is restored. For example, let the initial volume of fluid in each compartment be $V(0)$ and the initial concentration $c(0)$, then, if the mass of solute added to compartment B is M, the final equilibrium concentration will be

$$c(\infty) = c(0) + M/[2\,V(0)],$$

and the final volumes will be

$$V_A(\infty) = V(0)c(0)/c(\infty),$$

and

$$V_B(\infty) = V(0)[2 - c(0)/c(\infty)].$$

As the solution in volume B expands it does work on the solution in volume A.

Energetically the situation is as illustrated in Fig. 6, in which volumes A and B are fitted with movable pistons. Overall, the system is *not* reversible unless the process by which solute is supplied to volume B is reversible.

If the system is modified so continuous flow is possible (Fig. 7) the membrane permeabilities remaining unchanged, compartment B becoming the central core and A the descending flow, and solute is supplied continuously to the core at rate T_M; water will be osmotically withdrawn from the descending flow to enter the central core. As water leaves the descending flow the remaining solution will be concentrated, and as water enters the core it will dilute the core contents and give rise to an ascending counterflow that washes the solute out of the core. At equilibrium the total solute in the core will reach a constant value, which requires that the rate at which solute is being supplied to the core must equal the rate at which solute is being swept out by the entering water flow. Thus, (if axial diffusion in the core is small relative to the bulk flow) the relation

$$-F_{4v}(0)c_{4M}(0) = T_M, \tag{20}$$

must be satisfied, where $F_{4v}(0)$ is the total volume flow leaving the core at $x = 0$ and $c_{4M}(0)$ is the total core solute concentration at $x = 0$. (We introduce the subscripting convention: DHL corresponds to 1, AHL to 2, CD to 3, and core to 4.) The volume flow leaving the core is the difference between the volume flow entering the descending flow tube and the volume flow leaving it, or

$$-F_{4v}(0) = F_{1v}(0) - F_{1v}(L). \tag{21}$$

(In both of the above equations $F_{4v}(0)$ is negative by our sign convention.)

If solute neither enters nor leaves the descending flow, the product $F_{1v}(x)c_{1M}(x)$ is constant; in particular

$$F_{1v}(L)c_{1M}(L) = F_{1v}(0)c_{1M}(0). \tag{22}$$

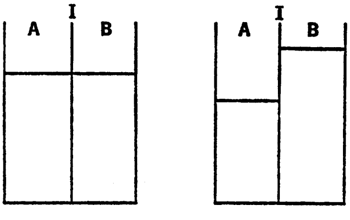

FIGURE 5

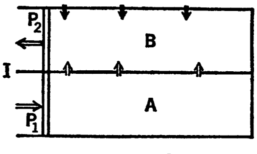

FIGURE 6

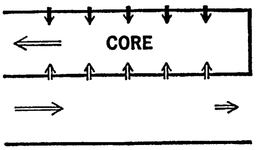

FIGURE 7

FIGURE 5 Membrane I separating A and B is water permeable, solute impermeable. Diagram illustrates effect of increasing total solute in B by one-half.

FIGURE 6 Showing system of Fig. 5 fitted with movable pistons. Solute is supplied to B; as solution in B expands it does useful work of concentration on solution in A.

FIGURE 7 Prototype of central core water-extracting system. Solute is supplied continuously to the core at total rate T_M. Water is extracted from descending flow.

From Eq. 22 the concentration ratio is given by

$$r = c_{1M}(L)/c_{1M}(0) = F_{1v}(0)/F_{1v}(L). \tag{23}$$

From Eqs. 23 and 21 we obtain

$$-F_{4v}(0) = F_{1v}(0)[1 - 1/r], \tag{24}$$

and from Eqs. 24 and 20

$$F_{1v}(0)[1 - 1/r]c_{4M}(0) = T_M. \tag{25}$$

The core concentration must be somewhat greater than the concentration in descending flow at a given position along the membrane separating the two flows, if water is to move by osmosis from descending flow to core. The average difference $\hat{\Delta}c$ must be large enough so that

$$-F_{4v}(0) = h_{14,v}L\hat{\Delta}c, \tag{26}$$

where $h_{14,v}$ is the hydraulic permeability per unit length of the membrane separating descending flow and the core.

A rough estimate of $\hat{\Delta}c$ can be obtained if we assume $c_{1M}(x) - c_{4M}(x)$ is the same order of magnitude everywhere, then

$$c_{4M}(0) \cong c_{1M}(0) + \hat{\Delta}c, \tag{27}$$

and substitution of Eq. 27 into Eq. 20 gives

$$h_{14,v}L\hat{\Delta}c[c_{1M}(0) + \hat{\Delta}c] \cong T_M, \tag{28}$$

whence

$$\hat{\Delta}c \cong T_M/[h_{14,v}Lc_{1M}(0)], \tag{29}$$

valid if $\hat{\Delta}c \ll c_{1M}(0)$. It is clear that Eq. 29 is not a very precise quantitative relation, but it does show that if

$$T_M/h_{14,v}L[c_{1M}(0)]^2 \ll 1, \tag{30}$$

then everywhere $c_{1M}(x) \cong c_{4M}(x)$. A more detailed analysis shows that this approximation improves as x increases from 0 to L, i.e. it is best in the region of greatest concentration. With this approximation valid, $c_{1M}(0)$ can be substituted for $c_{4M}(0)$ in Eq. 25 to give

$$r = 1/[1 - T_M/F_{1M}(0)], \tag{31}$$

where $F_{1M}(0) = F_{1v}(0)c_{1M}(0)$ is the entering solute load in the descending flow.

Since the essential approximation by which Eq. 31 is derived is the substitution of $F_{1M}(0)$ for $F_{1v}(0)c_{4M}(0)$, and $F_{1M}(0)$ is smaller than the product for which it is substituted, the actual concentration ratio will be somewhat smaller than that given by Eq. 31. It is also clear from Eqs. 20 and 21 that since $-F_{4v}(0)$ is always less than $F_{1v}(0)$, if T_M exceeds $F_{1M}(0)$, the approximation breaks down very rapidly. Nevertheless, Eq. 31 shows the crucial importance of the ratio of solute transport into the core to descending solute flow in determining the behavior of central core systems. It should be noted that in the derivation of Eq. 31 no assumptions whatsoever were introduced about the origin of the solute T_M supplied to the core, only that it was osmotically active solute without accompanying water. The coupled behavior of the core and descending flow tube will be the same whether the source is transport from the ascending flow, solute produced by some chemical reaction, or solute from some unidentified external reservoir.

The above analysis is easily extended to describe the behavior of the four tube system (Fig. 3) to which CD and ascending limb have been added. We will suppose a fraction f_U of the total descending flow (CD and DHL flow combined) is withdrawn from the system at $x = L$ as CD flow, and the remainder $(1 - f_U)$ is reflected by the hairpin bend as AHL flow. We will assume that the membranes separating descending flow and core remain permeable to water and impermeable to solute, and that the membrane separating ascending flow and core is impermeable to water but can transport solute. About the transport we will assume only that a fraction f_T of the solute that enters the ascending flow at $x = L$ is transported into the core and will assume nothing whatsoever about pump kinetics or back leak or even about the distribution of the source along the membrane separating ascending flow from core. We have for the axial solute flow entering the ascending flow tube

$$-F_{2M}(L) = (1 - f_U)F_{1M}(L), \tag{32}$$

and for transport into the core

$$T_M = -f_T F_{2M}(L). \tag{33}$$

Since $F_{1M}(L) = F_{1M}(0)$, no solute entering or leaving the descending flow because of the assumed membrane properties, Eqs. 32 and 33 combine to give

$$T_M = f_T(1 - f_U)F_{1M}(0). \tag{34}$$

Since no water enters the core from the ascending flow, Eq. 31 remains valid, and T_M from Eq. 34 can be substituted into it to give for the concentration ratio $c_{1M}(L)/c_{1M}(0)$,

$$r = 1/[1 - f_T(1 - f_U)]. \tag{35}$$

CENTRAL CORE SOLUTE-CYCLING ENGINE

In this section we derive equations for the central core system in a solute cycling mode of operation. Operationally, this is equivalent to the concentrating system suggested by Kuhn and Ramel (1959 *a*, *b*). Although we retain the central core in this mode, it serves only as a conduit for the transverse movement of solute and water, with no axial flow. Thus, there is no return of solution to the systemic circulation. Clearly, in this case, deletion of the central core will not alter the mathematical analysis.

Solute is pumped from AHL to core. Here it raises the concentration slightly. We suppose the DHL is so highly permeable to solute that there is no water extraction into the core, and part of the solute pumped from AHL enters the DHL to be recycled, and the rest enters the CD to raise the concentration of its fluid. At the loop end the collecting duct flow is $F_{3v}(L)$. This is a fraction f_U of the total descending flow. Thus,

$$f_U = F_{3v}(L)/[F_{1v}(L) + F_{3v}(L)]. \tag{36}$$

The ascending flow is given by

$$F_{2v}(L) = -(1 - f_U)[F_{1v}(L) + F_{3v}(L)]. \tag{37}$$

We suppose the AHL is water impermeable; hence,

$$F_{2v}(x) = F_{2v}(L). \tag{38}$$

By our assumption

$$F_{4v}(x) = 0. \tag{39}$$

By Eq. 18

$$F_{1v}(x) + F_{2v}(x) + F_{3v}(x) + F_{4v}(x) = F_{1v}(0) + F_{2v}(0) + F_{3v}(0) + F_{4v}(0). \tag{40}$$

Therefore, by Eqs. 38 and 39,

$$F_{1v}(x) + F_{3v}(x) = F_{1v}(0) + F_{3v}(0) \equiv F_{1v} + F_{3v}. \tag{41}$$

The point of Eq. 41 is that given Eqs. 39 and 38, the details of solute and water transfer between CD and DHL can be ignored for many purposes.

We have the general relation

$$J_{1M}(x) + J_{3M}(x) + J_{4M}(x) + J_{2M}(x) = 0. \tag{42}$$

Under our assumptions, $J_{4M}(x) = 0$. We will also assume J_{2M} is constant. Therefore,

$$J_{1M}(x) + J_{3M}(x) = -J_{2M}. \tag{43}$$

From Eq. 3 we have

$$\mathrm{d}(F_{1v}c_{1M})/\mathrm{d}x = -J_{1M}, \tag{44}$$

and

$$\mathrm{d}(F_{3v}c_{3M})/\mathrm{d}x = -J_{3M}. \tag{45}$$

Adding Eqs. 44 and 45, introducing the assumption that $c_{1M} \cong c_{3M}$, and using Eqs. 43 and 41 we obtain

$$[F_{1v}(0) + F_{3v}(0)]c_{1M}(x) = [F_{1v}(0) + F_{3v}(0)]c_{1M}(0) + J_{2M}x. \tag{46}$$

For AHL we have the equation

$$-F_{2v}(0)c_{2M}(x) = -F_{2v}(0)c_{2M}(L) - J_{2M}(L - x). \tag{47}$$

From Eqs. 46 and 47 concentrations are given by

$$c_{1M}(x) = c_{1M}(0) + J_{2M}x/[F_{1v} + F_{3v}], \tag{48}$$

and

$$c_{2M}(x) = c_{2M}(L) + J_{2M}(L - x)/F_{2v}. \tag{49}$$

From Eq. 48 we can write

$$c_{1M}(L) = c_{1M}(0) + J_{2M}L/[F_{1v} + F_{3v}]. \tag{50}$$

From Eqs. 50 and 36 follows

$$1 = \frac{c_{1M}(0)}{c_{1M}(L)} + \frac{J_{2M}L(1 - f_U)}{F_{1v}(L)c_{1M}(L)}. \tag{51}$$

Again defining $f_T = J_{2M}L/[F_{1v}(L)c_{1M}(L)]$, we obtain from Eq. 51 for the concentration ratio, $c_{1M}(L)/c_{1M}(0)$,

$$r = 1/[1 - f_T(1 - f_U)], \tag{52}$$

which is identical with Eq. 35.

From Eq. 49 we obtain

$$c_{1M}(L) - c_{2M}(0) = J_{2M}L/F_{1v}, \tag{53}$$

from which

$$1 - [c_{2M}(0)/c_{1M}(0)][c_{1M}(0)/c_{1M}(L)] = f_T. \tag{54}$$

Eq. 54 can be rearranged to give

$$c_{2M}(0)/c_{1M}(0) = r(1 - f_T). \tag{55}$$

The linear dependence of $c_{1M}(x)$ and $c_{2M}(x)$ on distance along the axis of the system given by Eqs. 48 and 49 depends upon the assumption that the rate of transport of J_{2M} out of the AHL is constant, but the important relations Eqs. 52 and 55 do not. This will be shown in the following section, where they will be derived in a general way for systems concentrating by combination of solute cycling and water extraction. Here we will derive them directly.[2]

Particles in the combined flow of descending limb and CD at the loop can be classified according to the number of times they have been pumped or recycled. If leak from descending flow to ascending flow is negligible then the flux of particles reaching the loop that have never been cycled is $[F_{1v}(0) + F_{3v}(0)]c_{1M}(0)$. Of this flux a fraction f_U leaves the system in the CD final flow and a fraction $1 - f_U$ enters the ascending limb. Of this, a fraction f_T is pumped and a fraction $1 - f_T$ leaves in the outflow of the ascending limb. Thus, the flux of particles reaching the loop that have been pumped once is

$$c_{1M}(0)[F_{1v}(0) + F_{3v}(0)]f_T(1 - f_U).$$

The total flux of particles reaching the loop in the combined descending flow is obtained by summing over all cyclings, or

$$[F_{1v}(0) + F_{3v}(0)]c_{1M}(L) = \sum_{n=0}^{\infty} [F_{1v}(0) + F_{3v}(0)]c_{1M}(0)[f_T(1 - f_U)]^n. \quad (56)$$

This geometric series sums to give

$$r = c_{1M}(L)/c_{1M}(0) = 1/[1 - f_T(1 - f_U)]. \quad (57)$$

Since $0 \leq f_T \leq 1$ and $0 \leq f_U \leq 1$, from Eq. 57 we obtain the limiting relations

$$r < 1/(1 - f_T), \quad (58)$$

and

$$r < 1/f_U. \quad (59)$$

Total efflux from the ascending limb is easily shown to be

$$F_{2v}(0)c_{2M}(0) = -[F_{1v} + F_{3v}]c_{1M}(0)\,\frac{(1 - f_T)(1 - f_U)}{1 - f_T(1 - f_U)}. \quad (60)$$

From Eq. 60 we obtain

$$c_{2M}(0)/c_{1M}(0) = (1 - f_T)/[1 - f_T(1 - f_U)], \quad (61)$$

---

[2] This derivation was first presented to the Biometrics Society, Atlanta, Georgia, April 1967.

which immediately reduces to Eq. 55. The above analysis not only gives considerable insight into the recycling system, but is of interest because it can be extended to transient problems (Stephenson, 1968, 1969).

Eqs. 52 and 55 are essentially mass balance relations. They remain valid for mixed operation central core systems in which concentration results from combined solute cycling and water extraction. These systems will be discussed in the following section.

MIXED OPERATION CENTRAL CORE ENGINES

In the system analyzed in this section, the configuration remains the same with three flow tubes grouped around the central core (Figs. 3 and 4). The system is fully connected in that every flow tube is in contact with every other flow tube. As we noted above, four is the maximum number of tubes that can be in mutual contact along their entire length. The membranes bounding the ascending limb are water impermeable; otherwise solute and water transport can occur across all membranes, permitting concentration to occur by a mixture of solute cycling and water extraction.

The equations describing solute flow in the system are (see Eq. 3)

$$dF_{iM}/dx = -J_{iM} \qquad (i = 1, 2, 3, 4), \tag{62}$$

with the subscripting convention descending limb, 1; ascending limb, 2; withdrawal tube, 3; and core, 4. Adding Eqs. 62 for $i = 1, 3, 4$; we obtain

$$d(F_{1M} + F_{3M} + F_{4M})/dx = -(J_{1M} + J_{3M} + J_{4M}). \tag{63}$$

We again assume the hydraulic permeabilities of the membranes separating descending flows from the core are sufficiently large that

$$c_{1M} \cong c_{3M} \cong c_{4M}, \tag{64}$$

and that axial diffusion can be neglected so that

$$F_{iM} = F_{iv}c_{iM}. \tag{65}$$

Eq. 65 is a good approximation except in the central core where it represents a highly idealized situation, which is, however, an important limiting case. From Eq. 18 and the boundary conditions $F_{1v}(L) = -F_{2v}(L)$ and $F_{4v}(L) = 0$ we have,

$$\sum_{i=1}^{i=4} F_{iv}(x) = \sum_{i=1}^{i=4} F_{iv}(L) = F_{3v}(L). \tag{66}$$

No water enters or leaves the ascending limb; hence,

$$F_{2v}(x) = -F_{1v}(L). \tag{67}$$

From Eqs. 66 and 67 we obtain the important relation,

$$F_{1v}(x) + F_{3v}(x) + F_{4v}(x) = F_{1v}(L) + F_{3v}(L). \tag{68}$$

Substitution of Eq. 65 into Eq. 63 and utilization of Eqs. 64, 65, and 68 gives the fundamental differential equation

$$[F_{1v}(L) + F_{3v}(L)](\mathrm{d}c_{4M}/\mathrm{d}x) = J_{2M}. \tag{69}$$

From Eqs. 62, 65, and 67 we obtain for the concentration in the ascending limb the equation

$$F_{1v}(L)(\mathrm{d}c_{2M}/\mathrm{d}x) = J_{2M}. \tag{70}$$

Together Eqs. 69 and 70 determine concentrations in all flow tubes, provided membrane permeabilities are such that Eqs. 64 and 67 are satisfied.[3] Although derived here for single solute systems, Eqs. 69 and 70 remain valid for *total* solute concentration in multisolute systems. It should be noted that $F_{1v}(L)$ and $F_{3v}(L)$ may or may not be given as boundary conditions. If not given, they are parameters of integration which must be adjusted so that the given boundary conditions are satisfied. This adjustment can give a seemingly trivial problem a Gorgonian head.

From Eqs. 69 and 70 we obtain the relation between c_{2M} and c_{4M},

$$\mathrm{d}c_{4M}/\mathrm{d}c_{2M} = F_{1v}(L)/[F_{1v}(L) + F_{3v}(L)]; \tag{71}$$

this has the integrated form

$$c_{4M}(x_2) - c_{4M}(x_1) = (1 - f_V)[c_{2M}(x_2) - c_{2M}(x_1)], \tag{72}$$

where x_2 and x_1 are arbitrary positions along the axis and f_V is as defined above. Integration of Eq. 69 gives

$$[F_{1v}(L) + F_{3v}(L)][c_{4M}(x) - c_{4M}(0)] = \int_0^x J_{2M}\,\mathrm{d}x. \tag{73}$$

From Eq. 73 we derive

$$[F_{1v}(L) + F_{3v}(L)]c_{4M}(L)[1 - 1/r] = T_{2M}, \tag{74}$$

which yields

$$r = \frac{1}{1 - T_{2M}/[F_{1M}(L) + F_{3M}(L)]}. \tag{75}$$

---

[3] Formally Eqs. 69 and 70 are identical with the differential equations for a single loop system with descending flow $F_{1v}(L) + F_{3v}(L)$ and ascending flow $-F_{1v}(L)$.

In Eqs. 74 and 75

$$T_{2M} = \int_0^L J_{2M}\,\mathrm{d}x, \tag{76}$$

is net total transport out of the ascending limb; also in these equations by Eq. 64 we have $r = c_{4M}(L)/c_{4M}(0) = c_{1M}(L)/c_{1M}(0) = c_{3M}(L)/c_{3M}(0)$ and $F_{1M}(L) = F_{1v}(L)c_{1M}(L) = F_{1v}(L)c_{4M}(L)$, with similar relations for $F_{3M}(L)$.

Integration of Eq. 62 gives

$$F_{1M}(L) = F_{1M}(0) - T_{1M}, \quad F_{3M}(L) = F_{3M}(0) - T_{3M}, \tag{77}$$

where T_{1M} and T_{3M} are net total transport integrals given by

$$T_{1M} = \int_0^L J_{1M}\,\mathrm{d}x, \qquad T_{3M} = \int_0^L J_{3M}\,\mathrm{d}x. \tag{78}$$

Substitution of $F_{1M}(L)$ and $F_{3M}(L)$ from Eq. 77 into Eq. 75 gives for the concentration ratio

$$r = \frac{1}{1 - T_{2M}/[F_{1M}(0) - T_{1M} + F_{3M}(0) - T_{3M}]}. \tag{79}$$

Eq. 79 is the fundamental mass balance equation for central core systems. It requires modification to account for diffusive loss of solute and other dissipative effects, but it manifests the basic role ployed by transport out of the various flow tubes. Although it has been derived for single solute systems, it remains valid for total solute balance in multisolute systems. It can, of course, be derived from overall mass balance by an extension of the analysis of the preceding section. It should be remembered that the transport integrals T_{1M}, T_{2M}, and T_{3M} are net total solute transport *out* of descending limb, ascending limb, and the tube corresponding to CD. By our sign convention $F_{1M}(0) > 0$ and $F_{3M}(0) > 0$, and physically T_{1M} and T_{3M} must be less than the entering solute flow. Therefore, $[F_{1M}(0) - T_{1M} + F_{3M}(0) - T_{3M}] > 0$. Thus, for the system to concentrate, i.e. $r > 1$, T_{2M} must be positive; if $T_{2M} = 0$, $r = 1$, and if $T_{2M} < 0$, $r < 1$. If T_{2M} is positive it must be less than $F_{1M}(L)$, therefore $T_{2M}/[F_{1M}(0) - T_{1M} + F_{3M}(0) - T_{3M}] < 1$. If T_{2M} is fixed at some positive value, then transport out of either descending flow, i.e. $T_{1M} > 0$, or $T_{3M} > 0$, will decrease the sum of the bracketed terms and increase r. Conversely, transport into either descending flow will decrease r. Specifically, if a fraction f_C of the solute transported out of the ascending flow enters the descending limb to be recycled, there being no other solute transport into or out of the descending limb so that $T_{1M} = -f_C T_{2M}$; the concentration ratio will be given by

$$r = \frac{1}{1 - T_{2M}/[F_{1M}(0) + f_C\,T_{2M} + F_{3M}(0) - T_{3M}]}. \tag{80}$$

If T_{2M} is fixed [it is assumed that $F_{1M}(0)$ and $F_{3M}(L)$ remain constant], then as f_C increases from 0 to 1 in Eq. 80, r will decrease monotonically. As f_C increases, however, T_{2M} can also increase as long as it satisfies $T_{2M} < F_{1M}(0) + f_C T_{2M}$. If T_{2M} does not remain constant but increases toward its limiting value $F_{1M}/[1 - f_C]$, then the concentration ratio will increase toward the limit given by

$$r_{\lim} = \frac{1}{1 - 1/[1 + (1 - f_C)F_{3M}(L)/F_{1M}(0)]}. \tag{81}$$

This limit clearly increases as f_C increases. Depending then on the concomitant change in T_{2M}, an increase in the recycling fraction may increase or decrease the concentration ratio, or leave it unchanged.

CANONICAL MASS BALANCE EQUATION

To cast the mass balance Eq. 75 into canonical form we define the withdrawal fraction f_U by

$$f_U = F_{3v}(L)/[F_{1v}(L) + F_{3V}(L)], \tag{82}$$

and the fractional transport f_T by

$$f_T = T_{2M}/F_{1M}(L). \tag{83}$$

From Eq. 82 by Eqs. 64 and 65 we obtain

$$1 - f_U = F_{1M}(L)/[F_{1M}(L) + F_{3M}(L)]. \tag{84}$$

Substituting from Eqs. 83 and 84 into Eq. 75 gives the dimensionless equation for the concentration ratio

$$r = 1/[1 - f_T(1 - f_U)]. \tag{85}$$

This equation is identical with Eqs. 35 and 52. It is the characteristic operating equation for a central core engine.

The characteristic equation determines a surface which we will call the operating surface or characteristic surface of the central core engine. Any triple (r, f_T, f_U) must lie on this surface, and given any two of the variables, the third can be found.

The portion of the surface determined by Eq. 85 in which we are interested is restricted by the domain of physical definition of f_U and f_T, namely $0 \leq f_U \leq 1$ and $f_T \leq 1$. We will only consider the concentrating engine so that f_T is further restricted to the domain $0 \leq f_T \leq 1$. In the specified domain it can be seen that $1 \leq r < \infty$. The various partial derivatives are of interest. These are:

$$[\partial r/\partial f_T]_{f_U} = r^2(1 - f_U), \tag{86}$$

$$[\partial r/\partial f_U]_{f_T} = -r^2 f_T, \tag{87}$$

$$[\partial f_T/\partial f_U]_r = f_T/(1 - f_U). \tag{88}$$

Thus in the specified domain of f_U and f_T, $(\partial r/\partial f_T) > 0$, except for $f_U = 1$, when $r = 1$ and $(\partial r/\partial f_T) = 0$, and $(\partial r/\partial f_U)$ is negative except for $f_T = 0$, when again $r = 1$ and $(\partial r/\partial f_U) = 0$. The derivative $(\partial f_T/\partial f_U)_r$ is positive, which means that if the withdrawal f_U increases there must be a compensatory increase in f_T if r is to remain constant. From Eq. 86 (or by inspection from Eq. 85) it is clear that for given f_U the maximum limit for the concentration ratio is found by setting $f_T = 1$ in Eq. 85; thus,

$$r < 1/f_U. \tag{89}$$

Similarly for given f_T, the limit is given by $f_U = 0$, when

$$r < 1/(1 - f_T). \tag{90}$$

If both $f_T = 1$ and $f_U = 0$, r is not defined, r becoming arbitrarily large if $f_T \to 1$ and $f_U \to 0$ simultaneously. Precisely, if $1 - f_T + f_U < \epsilon$, then $r > 1/\epsilon$.

In Fig. 8, the concentration ratio is plotted as a function of f_T for various values of f_U. These plots are, of course, identical with those for r as a function of $(1 - f_U)$

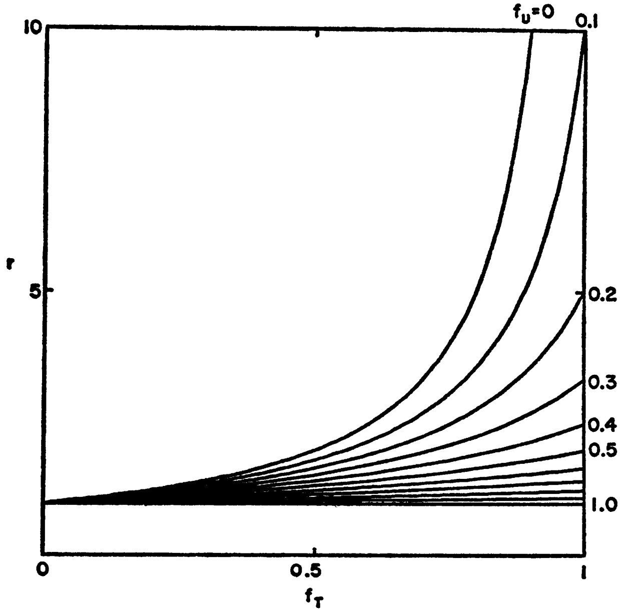

FIGURE 8 Concentration ratio r plotted against fractional transport f_T for different values of fractional urine flow f_U.

for different values of $1 - f_T$, because of the obvious symmetry of Eq. 85 with respect to f_T and $1 - f_U$. A different projection of the operating surface is obtained by rearranging Eq. 85 to the form

$$(r - 1)/r = f_T(1 - f_U). \tag{91}$$

From Eq. 91 we obtain the important limiting relations

$$1 - 1/r \leq f_T \leq 1, \tag{92}$$

and

$$0 \leq f_U \leq 1/r. \tag{93}$$

In Fig. 9 the transport fraction f_T is plotted against f_U for several values of r. In utilizing the characteristic surface for the analysis of central core engines it should be realized that if one of the variables, say f_U, changes, in general both of the others will change, and the operating path followed by the system will not lie in a plane parallel to one of the coordinate planes but will be some skew curve lying on the characteristic surface. Hence, none of the plane curves plotted in Figs. 8 and 9 would be a projection of an operating curve under most circumstances. The analysis given in this section applies with slight modification to multisolute systems and systems in which there is dissipative loss of solute from the central core.

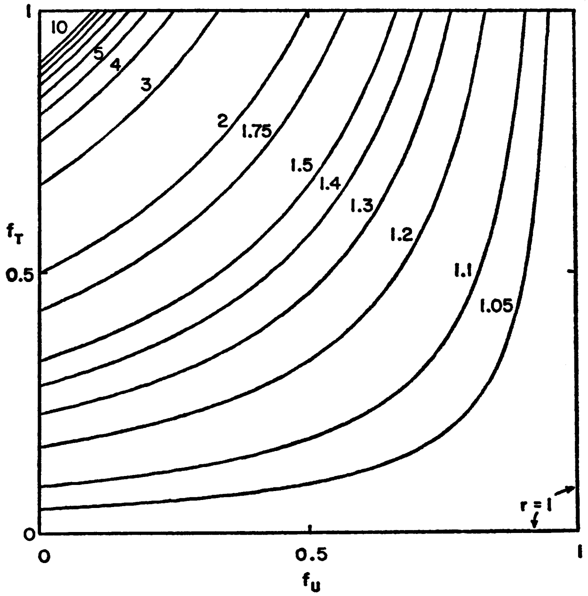

FIGURE 9 Fractional transport rate plotted against fractional urine flow for different values of the concentration ratio. This gives another projection of the characteristic surface.

CONCENTRATION PROFILES

In order to integrate Eqs. 69 and 70 and so obtain c_{2M} and $c_{4M} \cong c_{1M} \cong c_{3M}$ as functions of x, the net outward solute flux J_{2M} must be known as a function of c_{1M}, c_{2M}, c_{3M}, and c_{4M}. If it is, solution by quadrature is always possible as we will show below, but certain qualitative features of the concentration profiles can be deduced without actually carrying out the quadrature. If $J_{2M} > 0$ for all x, then Eqs. 69 and 70 show that all concentrations increase monotonically with x. If $J_{2M} = 0$, the concentration gradients in all flows equal 0, and if $J_{2M} < 0$, then $\mathrm{d}c_{iM}/\mathrm{d}x < 0$, for all i and all x.

Of considerable interest is the concentration difference between ascending flow and the core and descending flows, because this determines the chemical potential difference against which solute must be transported in a single solute system. From Eq. 72

$$\frac{c_{2M}(L) - c_{2M}(x)}{c_{4M}(L) - c_{4M}(x)} = \frac{1}{1 - f_U}. \tag{94}$$

Subtracting 1 from both sides of Eq. 94 and using the boundary condition $c_{2M}(L) = c_{1M}(L) \cong c_{4M}(L)$ gives us

$$\frac{c_{4M}(x) - c_{2M}(x)}{c_{4M}(L) - c_{4M}(x)} = \frac{f_U}{1 - f_U}. \tag{95}$$

Integration of Eq. 69 to give $c_{4M}(L) - c_{4M}(x)$ and substitution into Eq. 95 yields

$$c_{4M}(x) - c_{2M}(x) = \frac{f_U}{1 - f_U} \frac{\int_x^L J_{2M}\,\mathrm{d}x}{F_{1v}(L) + F_{3v}(L)} \tag{96}$$

By our assumptions $f_U/\{(1 - f_U)[F_{1v}(L) + F_{3v}(L)]\}$ is positive, therefore, $c_{4M}(x) - c_{2M}(x)$ has the sign of $\int_x^L J_{2M}\,\mathrm{d}x$. If $J_{2M} > 0$ for all x, then $c_{4M}(x) - c_{2M}(x)$ decreases monotonically from its maximum value

$$c_{4M}(0) - c_{2M}(0) = f_U f_T r c_{4M}(0), \tag{97}$$

at $x = 0$ to 0 at $x = L$. If $f_U = 0$, i.e. if there is no withdrawal of concentrated solution from the system, then we have $c_{2M}(x) = c_{4M}(x)$ everywhere. From Eq. 97 we obtain

$$\begin{aligned} c_{2M}(0)/c_{4M}(0) &= r(1 - f_T) = (1 - rf_U)/(1 - f_U) \\ &= 1 - rf_U f_T, \end{aligned} \tag{98}$$

frequently used relations.

To integrate Eqs. 69 and 70, let J_{2M} be a known function of the concentrations, but not an explicit function of x, i.e.,

$$J_{2M} = \phi(c_{1M}, c_{2M}, c_{3M}, c_{4M}). \tag{99}$$

Then by Eq. 64

$$J_{2M} = \phi(c_{2M}, c_{4M}). \tag{100}$$

By Eq. 94 one of c_{2M} or c_{4M} can be eliminated from Eq. 100, e.g.,

$$c_{4M}(x) = (1 - f_U)c_{2M}(x) + f_U c_{4M}(L). \tag{101}$$

We then have from Eqs. 100, 101, and 70

$$\frac{F_{1v}(L)\, \mathrm{d}c_{2M}}{\phi[c_{2M}, (1 - f_U)c_{2M} + f_U\, c_{4M}(L)]} = \mathrm{d}x, \tag{102}$$

from which

$$x = F_{1v}(L) \int_0^x \frac{\mathrm{d}c_{2M}}{\phi}, \tag{103}$$

where ϕ is a function only of $c_{2M}(x)$, but contains the parameters of integration f_U and $c_{4M}(L)$, which may not be given.

For certain cases of interest Eq. 103 can be integrated analytically. The first is for ϕ constant. This is a useful approximation if J_{2M} does not vary too greatly with distance along the axis of the system. Then we can take ϕ to be the mean value of J_{2M} or

$$\phi = \int_0^L J_{2M}\, \mathrm{d}x/L. \tag{104}$$

Then from Eq. 103

$$c_{2M}(x) = c_{2M}(0) + \phi x/F_{1v}(L), \tag{105}$$

and

$$c_{4M}(x) = c_{4M}(0) + \phi x/[F_{1v}(L) + F_{3v}(L)]. \tag{106}$$

Eqs. 105 and 106 show that for a constant source J_{2M} the concentration in all flow tubes increases linearly from cortex to papilla.

A second case that can be integrated explicitly is when solute is actively transported from ascending limb to core. We will suppose the "pump" obeys approximate Michaelis-Menten kinetics and back leak is by passive diffusion. Then

$$J_{2M} = \frac{a}{1 + b/c_{2M}} - h_M(c_{4M} - c_{2M}), \tag{107}$$

where a is the maximum rate of the active transport, b is the Michaelis constant, and h_M is the permeability per unit length of the ascending limb. Substituting c_{4M} from Eq. 101 into Eq. 107 gives

$$\phi = \frac{a}{1 + b/c_{2M}(x)} - f_U\, h_M[c_{4M}(L) - c_{2M}(x)]. \tag{108}$$

If the pump is saturated

$$\phi = a - f_U h_M[c_{4M}(L) - c_{2M}(x)]. \tag{109}$$

Substitution of Eq. 109 into Eq. 103 gives after integration the solution

$$x = \frac{F_{1v}(L)}{B} \ln \frac{A + Bc_{2M}(x)}{A + Bc_{2M}(0)}, \tag{110}$$

where $A = a - f_U h_M c_{4M}(L)$, and $B = f_U h_M$. From Eq. 110 we obtain

$$[A + Bc_{2M}(0)] = a\cdot\exp[-BL/F_{1v}(L)], \tag{111}$$

and from Eqs. 110 and 111

$$c_{2M}(x) = c_{4M}(L) - (a/B)\{1 - \exp[-B(L - x)/F_{1v}(L)]\}. \tag{112}$$

From Eqs. 112 and 101 we obtain

$$c_{4M}(x) = c_{4M}(L) - (1 - f_U)(a/B)\{1 - \exp[-B(L - x)/F_{1v}(L)]\}. \tag{113}$$

From Eq. 112 we obtain

$$c_{4M}(L) - c_{2M}(0) = (a/B)\{1 - \exp[-BL/F_{1v}(L)]\}. \tag{114}$$

Multiplication of both sides of Eq. 114 by $F_{1v}(L)$ gives

$$\int_0^L J_{2M}\, \mathrm{d}x = F_{1v}(L)(a/B)\{1 - \exp\,[-BL/F_{1v}(L)]\}. \tag{115}$$

From Eq. 115 the fractional transport out of the ascending limb is

$$f_T = \frac{\int_0^L J_{2M}\, \mathrm{d}x}{F_{1v}(L)c_{2M}(L)} = \frac{a}{f_U\, h_M\, c_{2M}(L)}\left\{1 - \exp\left[-\frac{f_U\, h_M\, L}{F_{1v}(L)}\right]\right\}. \tag{116}$$

From Eq. 116 it follows that as $f_U h_M \rightarrow 0$, $f_T \rightarrow aL/F_{1v}c_{2M}(L)$, this will occur if either $f_U \rightarrow 0$ or $h_M \rightarrow 0$. It is obvious that if $h_M = 0$ there will be no back leak, but that the effect of back leak also depends on f_U may at first glance seem strange. The reader will recall, however, that the difference $c_{4M}(x) - c_{2M}(x)$ goes to zero for all x as $f_U \rightarrow 0$. Thus, the leak becomes inoperative. A quantitative description of the effect of back leak is obtained by defining the dimensionless factor

$$\gamma = f_U h_M L/F_{1v}(L), \tag{117}$$

then

$$f_T = \frac{aL}{F_{1v}(L)c_{2M}(L)}(1 - e^{-\gamma})/\gamma. \tag{118}$$

As γ goes from 0 to ∞, the factor $(1 - e^{-\gamma})/\gamma$ goes from 1 to 0. The *total* solute pumped out of the ascending limb is aL. Of this the net fraction

$$f_L = (\gamma - 1 + e^{-\gamma})/\gamma, \tag{119}$$

leaks back to leave the system via the ascending limb. The concentration ratio is given by

$$r = 1/[1 - (1 - f_U)f_T{}^0(1 - f_L)], \tag{120}$$

where $f_T{}^0 = aL/[F_{1v}(L)c_{2M}(L)]$ is the fractional transport with no back leak; f_L is plotted as a function of γ in Fig. 10.

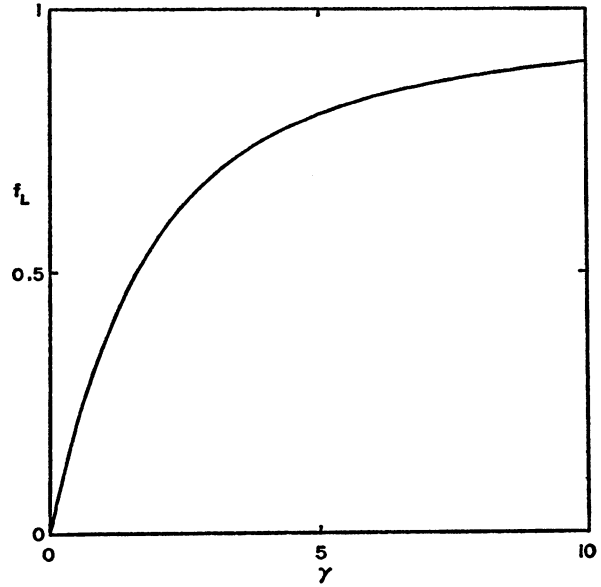

FIGURE 10 Fractional back leak plotted against the dimensionless parameter γ (see text).

If the pump is far from saturation, $b/c_{2M}(x) \gg 1$ and flux out of the ascending limb is given by

$$\phi = (a/b)c_{2M}(x) - f_U h_M[c_{4M}(L) - c_{2M}(x)], \tag{121}$$

again explicit integration is possible after substituting Eq. 121 into Eq. 103 and again

$$x = \frac{F_{1v}(L)}{B} \ln \frac{A + Bc_{2M}(x)}{A + Bc_{2M}(0)}, \tag{122}$$

where now

$$A = -f_U h_M c_{4M}(L), \tag{123}$$

and

$$B = [a/b + f_U h_M]. \tag{124}$$

In an analysis that differs only in details from that for the saturated system we find

$$c_{2M}(x) = \frac{(a/b)c_{4M}(L)}{B} \exp\left[-\frac{B(L-x)}{F_{1v}(L)}\right] + \frac{f_U\, h_M\, c_{4M}(L)}{B}, \tag{125}$$

and

$$c_{4M}(x) = c_{4M}(L)\left\{\frac{(1-f_U)(a/b)}{B} \exp\left[-\frac{B(L-x)}{F_{1v}(L)}\right] + \left[\frac{(1-f_U)f_U\, h_M}{B} + f_U\right]\right\}. \tag{126}$$

From Eqs. 125 and 126 we derive

$$\frac{c_{4M}(L)}{c_{4M}(0)} = \frac{1}{f_U + (1-f_U)\{(a/b)\exp[-BL/F_{1v}(L)] + f_U\, h_M\}/B}, \tag{127}$$

which gives the canonical form

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

with

$$f_T = 1 - (f_U h_M/B) - [a/(bB)] \exp[-BL/F_{1v}(L)]. \tag{128}$$

Eq. 128 reduces to

$$f_T = \gamma_0[1 - \exp(-\gamma)]/\gamma, \tag{129}$$

where

$$\gamma = [a/b + f_U h_M]L/F_{1v}(L), \tag{130}$$

and

$$\gamma_0 = (a/b)L/F_{1v}(L).$$

For $f_U h_M = 0$ we have

$$f_T^{\,0} = 1 - \exp(-\gamma_0). \tag{131}$$

In the general case, when flux out of the ascending limb is given by

$$\phi = \frac{a}{1 + b/c_{2M}(x)} - f_U\, h_M[c_{4M}(L) - c_{2M}(x)], \tag{132}$$

integration gives

$$\frac{2BL}{F_{1v}(L)}\frac{x}{L} = \ln\left\{\frac{[c_{2M}(x)]^2 + dc_{2M}(x) + e}{[c_{2M}(0)]^2 + dc_{2M}(0) + e}\right\} + \frac{2b - d}{q^{1/2}}\left[\ln\left\{\frac{2c_{2M}(x) + d - q^{1/2}}{2c_{2M}(x) + d + q^{1/2}}\right\} - \ln\left\{\frac{2c_{2M}(0) + d - q^{1/2}}{2c_{2M}(0) + d + q^{1/2}}\right\}\right], \tag{133}$$

where $B = f_U h_M$, $d = a/B + b - c_{4M}(L)$, $e = -bc_{4M}(L)$, and $q = d^2 - 4e$. Although Eq. 133 is of some computational use it cannot be inverted to give $c_{2M}(x)$ as an explicit function of x. When $h_M = 0$, we obtain the limiting expression from Eqs. 132 and 103

$$ax/F_{1v}(L) = c_{2M}(x) - c_{2M}(0) + b\ln[c_{2M}(x)/c_{2M}(0)]. \tag{134}$$

From this, using the relation

$$c_{4M}(0) = (1 - f_U)c_{2M}(0) + f_U c_{4M}(L), \tag{135}$$

or

$$c_{2M}(0)/c_{4M}(0) = (1 - rf_U)/(1 - f_U), \tag{136}$$

we derive

$$\frac{aL}{F_{1v}(L)} = c_{4M}(L) - c_{4M}(0)\,\frac{1 - rf_U}{1 - f_U} + b\ln\left\{\frac{r(1 - f_U)}{1 - rf_U}\right\}, \tag{137}$$

or

$$f_T^M = 1 - \frac{1 - rf_U}{(1 - f_U)r} + \frac{b}{c_{4M}(L)} \ln\left\{\frac{r(1 - f_U)}{1 - rf_U}\right\}, \tag{138}$$

where $f_T^M \equiv aL/[F_{1v}(L)c_{4M}(L)]$, i.e., f_T^M is the fractional transport out of the ascending limb at *saturation.* Eq. 138 gives the recursive relation for computing r.

$$r = 1/[1 - f_T(1 - f_U)], \tag{139}$$

where

$$f_T = f_T^M - [b/c_{4M}(L)] \log [r(1 - f_U)/(1 - rf_U)]. \tag{140}$$

It is clear that the number of possible cases is limitless. In Fig. 11, we have plotted concentration profiles for saturated, unsaturated, and partly saturated pump, with no back leak. In all cases, $r = 10$ and $f_U = 0.05$.

The discerning reader will have noted that the above equations contain $F_{1v}(L)$ and $F_{3v}(L)$ as parameters of integration. If these and $c_{4M}(L) = c_{2M}(L)$ are given, the problem is a straightforward initial value problem, and $c_{4M}(0)$ and $c_{2M}(0)$ can be computed from any of the variants of Eqs. 101 and 103, e.g., from Eqs. 134 and 135 given a and b. In some cases it is useful to look at the problem from this point

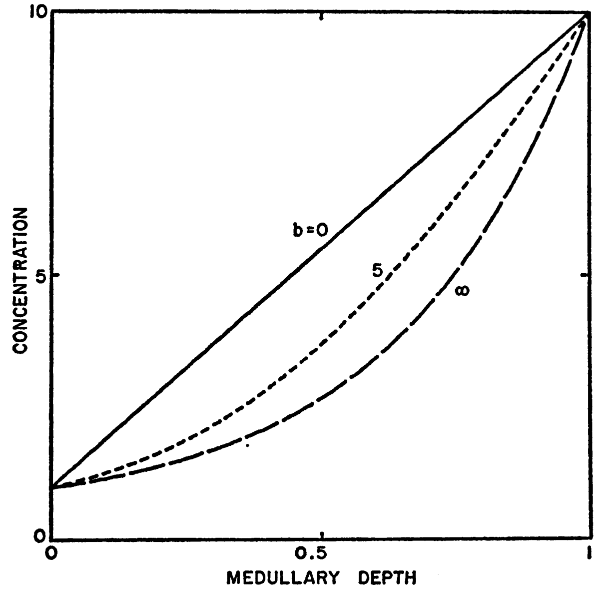

FIGURE 11 Concentration profile for different degrees of pump saturation and no back leak: $b = 0$ corresponds to saturation, $b = 5$ to half-saturation, and $b = \infty$ to unsaturation; $f_U = 0.05$ for all cases.

of view, but it should be noted that $F_{1v}(0)$ and $F_{3v}(0)$ cannot be computed without introducing more information into the problem. More typically $F_{1v}(0)$,$F_{3v}(0)$, and $c_{1M}(0) = c_{3M}(0) \simeq c_{4M}(0)$ are given together with the additional boundary conditions $F_{2v}(L) = -F_{1v}(L)$, $c_{2M}(L) \simeq c_{4M}(L)$, and $F_{4v}(L) = 0$. To be found are $c_{2M}(L) = c_{1M}(L) \simeq c_{4M}(L)$, $c_{2M}(0)$, $F_{1v}(L)$, and $F_{3v}(L)$. To solve this problem additional integrals are needed. To obtain these the details of transport from DHL and CD into the central core must be taken into account. We illustrate with a relatively simple example: a detailed analysis is in preparation. Let transport out of the ascending limb be given by

$$J_{2M} = a/[1 + b/c_{2M}(x)], \tag{141 a}$$

$$J_{2v} = 0, \tag{141 b}$$

transport out of the descending limb by

$$J_{1M} = h_{14,M}(c_{1M} - c_{4M}), \tag{142}$$

$$J_{1v} = h_{14,v}(c_{4M} - c_{1M}), \tag{143}$$

transport out of the CD by

$$J_{3M} = 0. \tag{144}$$

Integration of Eq. 3 for the CD gives by Eq. 144

$$F_{3M} = F_{3v}(x)c_{3M}(x) = F_{3v}(0)c_{3M}(0). \tag{145}$$

From Eq. 145 by Eq. 64

$$F_{3v}(x) = F_{3v}(0)c_{3M}(0)/c_{4M}(x). \tag{146}$$

From Eqs. 142 and 143 we obtain

$$\mathrm{d}(F_{1v}c_{1M})/\mathrm{d}F_{1v} = -h_{14,M}/h_{14,v}\,. \tag{147}$$

Thus,

$$F_{1v}(L)c_{1M}(L) - F_{1v}(0)c_{1M}(0) = (-h_{14,M}/h_{14,v})[F_{1v}(L) - F_{1v}(0)]. \tag{148}$$

Eqs. 142 and 143 essentially assume the reflection coefficient for DHL is 1. Reflection coefficients less than 1 are considered in the detailed discussion. Eq. 146 gives

$$F_{3v}(L) = F_{3v}(0)c_{3M}(0)/c_{4M}(L) = F_{3v}(0)/r. \tag{149}$$

From Eq. 148 we obtain

$$F_{1v}(L) = (g + 1)F_{1v}(0)/(g + r), \qquad (150)$$

where

$$g = h_{14,M}/[h_{14,v}c_{1M}(0)]. \qquad (151)$$

Substitution of Eqs. 149 and 150 into Eq. 82 gives

$$f_U = \frac{(g + r)F_{3v}(0)}{r(g + 1)F_{1v}(0) + (g + r)F_{3v}(0)}. \qquad (152)$$

Substitution of Eqs. 149, 150, and 152 into the various expressions derived above for concentrations in the core and ascending limb lead to equations that can be solved for r. For example, if we assume a completely saturated pump and no back leak, then from Eq. 109, $\phi = a$, and from Eq. 106

$$r = 1 + aL/\{c_{4M}(0)[F_{1v}(L) + F_{3v}(L)]\}. \qquad (153)$$

Substituting from Eqs. 149 and 150 we obtain

$$r = 1 + aL\bigg/\left\{c_{4M}(0)\left[\frac{F_{3v}(0)}{r} + \frac{(g + 1)F_{1v}(0)}{g + r}\right]\right\}. \qquad (154)$$

Eq. 154 reduces to a quadratic that can be solved to give r, and hence $F_{1v}(L)$ and $F_{3v}(L)$, as functions of a, L, $c_{4M}(0)$, $F_{1v}(0)$, $F_{3v}(0)$, and g. Substitution of the values of $F_{1v}(L)$ and $F_{3v}(L)$ so determined back into Eqs. 105 and 106 leads to a solution in terms of the boundary conditions and the membrane parameters.

The dependence of the solution of Eq. 154 on g can be determined by rearranging Eq. 154 to give

$$1 = \frac{c_{4M}(0)}{aL}\left[\frac{F_{3v}(0)}{1 + 1/(r - 1)} + \frac{F_{1v}(0)}{1/(g + 1) + 1/(r - 1)}\right]. \qquad (155)$$

It can be seen by inspection that Eq. 155 has a positive root $r > 1$ provided

$$c_{4M}(0)[F_{3v}(0) + (g + 1)F_{1v}(0)] > aL, \qquad (156)$$

and that this root decreases as g increases. Since solute cycling increases as g increases we again conclude that for a completely saturated pump the concentration ratio decreases with an increase in solute cycling.

As an another example, we will assume that the pump is unsaturated and there is no back leak; Eq. 137 then applies. For the simplified case $f_U = 0$, after substitution from Eq. 150 and rearrangement using the identity $(g + r)/(g + 1) = 1 + (r - 1)/$

$(g + 1)$, we obtain

$$aL/A = (r - 1)\left[1 - \frac{aL}{A(g + 1)}\right] + [b/c_{1M}(0)] \ln [1 + (r - 1)], \quad (157)$$

where we have made the substitution $A = F_{1v}(0)c_{1M}(0)$. From Eq. 148 we have

$$F_{1v}(L)c_{1M}(L) < (g + 1)A \quad (158)$$

from which it follows that

$$aL < F_{1v}(L)c_{1M}(L) < (g + 1)A. \quad (159)$$

The right-hand side of Eq. 157 equals 0 for $r = 1$, and with Eq. 159 satisfied increases monotonically with r for $r > 1$. Hence Eq. 157 has one real positive root greater than 1. Differentiation of Eq. 157 gives

$$\frac{\partial r}{\partial g} = -(r - 1) \frac{aL}{A(g + 1)^2} \Big/ \left\{\left[1 - \frac{aL}{A(g + 1)}\right] + \frac{b}{rc_{1M}(0)}\right\}, \quad (160)$$

from which it follows that in this case also r decreases as g increases. Again substitution of r, as determined by solving Eq. 157, into Eq. 150, leads to a solution of Eq. 134 for core and ascending limb concentrations, which are equal in this case. If $f_U \neq 0$ or if there is back leak into the ascending limb, the analysis becomes much more complicated and is deferred to a subsequent paper.

ENERGY REQUIREMENTS FOR CONCENTRATION

In a single solute central core engine the inflows into the descending limb and CD are separated into three outflows: that from the central core, that from the ascending limb, and that from the CD. By our assumptions the two inflows and the core outflow are isosmolar. The outflow of the CD is relatively concentrated, and that of the ascending limb is relatively dilute.

The following calculation shows that there is a net increase in the Gibbs free energy of a unit of outflow over the free energy of a unit of inflow. In dilute solutions the chemical potential of a solute is

$$\mu = \mu_c^0 + RT \ln c, \quad (161)$$

where R is the gas constant, T the absolute temperature, and μ_c^0 a constant for given temperature and pressure. The total free energy inflow per unit time is

$$\dot{G}_{\text{in}} = F_{1M}(0)[\mu_c^0 + RT \ln c_{1M}(0)] + F_{3M}(0)[\mu_c^0 + RT \ln c_{3M}(0)]. \quad (162)$$

The free energy of the outflow per unit time is

$$\dot{G}_{\text{out}} = -F_{4M}(0)[\mu_c^0 + RT \ln c_{4M}(0)] - F_{2M}(0)[\mu_c^0 + RT \ln c_{2M}(0)] + F_{3M}(L)[\mu_c^0 + RT \ln c_{3M}(L)]. \quad (163)$$

From Eqs. 162, 163, and 64 we obtain for $\Delta\dot{G} = \dot{G}_{\text{out}} - \dot{G}_{\text{in}}$

$$\Delta\dot{G} = RT\{F_{3M}(L) \ln c_{3M}(L) - F_{2M}(0) \ln c_{2M}(0) - [F_{1M}(0) + F_{3M}(0) + F_{4M}(0)] \ln c_{4M}(0)\}. \quad (164)$$

Using the mass balance relation

$$F_{1M}(0) + F_{3M}(0) + F_{2M}(0) + F_{4M}(0) = F_{3M}(L), \quad (165)$$

we can write Eq. 164

$$\Delta\dot{G} = RT\{F_{3M}(L) \ln [c_{3M}(L)/c_{1M}(0)] + F_{2M}(0) \ln [c_{1M}(0)/c_{2M}(0)]\}, \quad (166)$$

from which we derive by Eqs. 98, 82, and 83

$$\Delta\dot{G} = RT[F_{1M}(L) + F_{3M}(L)]\{f_U \ln r + (1 - f_U)(1 - f_T) \ln [r\,(1 - f_T)]\}. \quad (167)$$

From Eq. 167 we obtain, using the relation

$$r(1 - f_T) = (1 - rf_U)/(1 - f_U), \quad (168)$$

$$\Delta\dot{G} = RT[F_{1M}(L) + F_{3M}(L)]\{(\ln r)/r + [(1/r) - f_U] \ln (1 - f_T)\}. \quad (169)$$

If $f_U = 0$, then we have $r = 1/(1 - f_T)$, and it follows from Eq. 169 that $\Delta\dot{G} = 0$. Differentiation of Eq. 169 with respect to f_U gives

$$[\partial\Delta\dot{G}/\partial f_U]_r = RT[F_{1M}(L) + F_{3M}(L)] \cdot \left\{- \ln (1 - f_T) - \frac{1 - rf_U}{r(1 - f_T)} \left(\frac{\partial f_T}{\partial f_U}\right)_r\right\}, \quad (170)$$

which by Eq. 88 reduces to

$$[\partial\Delta\dot{G}/\partial f_U]_r = RT[F_{1M}(L) + F_{3M}(L)]\{-f_T - \log (1 - f_T)\} \quad (171)$$

Eq. 171 shows that for fixed r, $\Delta\dot{G}$ increases monotonically from 0 to the maximum $RT[F_{1M}(L) + F_{3M}(L)] (\ln r)/r$ as f_U increases from 0 to $1/r$.

It is clear that to effect this increase in the free energy of the outflow over the inflow requires that work be supplied from some external source. In the system we are considering this work is used to transport solute out of the ascending limb into the central core. At a given position x along the membrane separating ascending limb and core, this transport is against a chemical potential difference $RT \cdot \ln [c_{4M}(x)/c_{2M}(x)]$. Since the solute transported per unit length is $J_{2M}(x)$, the minimum total work required per unit time for membrane transport is

$$\Delta\dot{W} = RT \int_0^L J_{2M}(x) \ln [c_{4M}(x)/c_{2M}(x)]\, dx. \quad (172)$$

From Eq. 69 we have

$$J_{2M}(x)\mathrm{d}x = [F_{1v}(L) + F_{3v}(L)]\,\mathrm{d}c_{4M}. \tag{173}$$

and

$$J_{2M}(x)\,\mathrm{d}x = F_{1v}(L)\,\mathrm{d}c_{2M}. \tag{174}$$

The variable of integration in Eq. 172 can be changed by Eqs. 173 and 174 to give

$$\Delta\dot{W} = RT\Bigg\{[F_{1v}(L) + F_{3v}(L)] \cdot \int_{c_{4M}(0)}^{c_{4M}(L)} \ln c_{4M}\,\mathrm{d}c_{4M} - F_{1v}(L)\int_{c_{2M}(0)}^{c_{4M}(L)} \ln c_{2M}\,\mathrm{d}c_{2M}\Bigg\}. \tag{175}$$

Carrying out the integration in Eq. 175 and using the mass balance relation

$$[F_{1v}(L) + F_{3v}(L)]c_{4M}(0) = F_{3v}(L)c_{4M}(L) + F_{1v}(L)c_{2M}(0), \tag{176}$$

we obtain

$$\Delta\dot{W} = RT\{F_{3v}(L)c_{4M}(L)\ln[c_{4M}(L)/c_{4M}(0)] - F_{1v}(L)c_{2M}(0)\ln[c_{4M}(0)/c_{2M}(0)]\}, \tag{177}$$

which reduces to Eq. 166. Hence, we have $\Delta\dot{G} = \Delta\dot{W}$, or the *minimum* energy required per unit of time to effect the membrane transport exactly equal to the Gibbs free energy difference between outflow and inflow per unit time.

Subsequently, this result will be generalized to include dissipative terms and more than one solute. Its immediate significance in single solute systems is that it shows that there is no basic thermodynamic difference between solute cycling and water extracting modes of operation. The result, of course, says nothing about the efficiency with which metabolic energy is coupled to the membrane transport.

Computation of the minimum energy requirement for a given segment requires the solution of the differential equations describing the system to give $c_{2M}(x)$ and $c_{4M}(x)$. These are then substituted in the expression for $J_{2M}[c_{2M}(x), c_{4M}(x)]$. In Fig. 12 minimum energy requirements are plotted for saturated, unsaturated, and and partly saturated pump with no leak. Back leak, of course, increases the metabolic energy which must be supplied [by the factor $\gamma/(1 - e^{-\gamma})$] in the saturated pump, but $\Delta\dot{W}$ as calculated by Eq. 172 still equals $\Delta\dot{G}$ exactly. The most striking feature of the plots is the sharp decrease in energy requirements as $x \to L$, which reflects the fact that irrespective of the mechanism of transport, $c_{4M}(x)/c_{2M}(x) \to 1$ as $x \to L$.

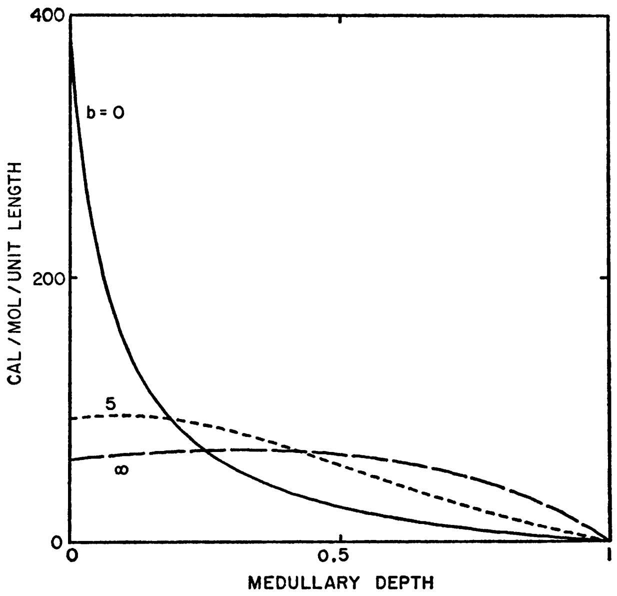

FIGURE 12 Minimum work requirements for transport out of the ascending limb per unit fractional length of the medulla for different pump saturations.

DISCUSSION

The representation of the renal medulla by an ideal single solute central core engine clearly has limitations. It does, however, make manifest certain features of the system that are obscured by the mathematical details of models that include the effects of several solutes, vascular washout, and finite permeabilities.

The relation (Eq. 79) showing the effects of solute transport out of ascending limb, descending limb, and CD remains valid for total solute transport in multisolute systems. Eq. 91, which shows that both f_T and $1 - f_U$ must be between 1 and $(r - 1)/r$, remains valid in multisolute systems and applies with slight modification to systems in which there is dissipative loss of solute from the central core because of inefficiency of the vascular exchanger.

The decrease in the ratio of core osmolality to ascending limb osmolality from $(1 - f_U)/(1 - rf_U)$ at the corticomedullary border to 1 at the papilla also remains valid in multisolute systems although no such generalization is possible about the ratio of individual solutes. It does, however, remain true that the energetic requirements of the inner medulla, for a given amount of solute transport, are much less than for the outer medulla.

The ideal single solute central core system has the same theoretical thermodynamic efficiency irrespective of the fraction of solute which is recycled in that $RT \int_0^L J_{2M} \ln [c_{4M}(x)/c_{2M}(x)]\, dx$ always exactly equals $\Delta \dot{G}$, the increase in Gibbs free energy of outflow over inflow per unit time. Since it has been assumed that

$c_{4M}(x) = c_{1M}(x) = c_{3M}(x)$, transport between core and descending limb or between core and CD does not contribute to $\Delta\dot{G}$. In a nonideal system in which $c_{4M}(x) > c_{1M}(x)$, a dissipative term is introduced by solute recycling and by water movement. The theoretical efficiency of various systems depends on the exact nature of these dissipative terms and will be discussed in a later paper.

It will be noted that the relation between the surface transport integrals and $\Delta\dot{G}$ says nothing about the efficiency with which metabolic energy can be coupled to the transport. Neither does it indicate that when back leak is introduced, dissipative loss of energy may occur. This solute leaking back is totally dissipative. For the saturated pump, the metabolic energy which must be supplied is $RT \quad a \quad \int_0^L \ln\,[c_{4M}(x)/c_{2M}(x)]\,\mathrm{d}x$.

One concept which emerges from the analysis of the single solute system is that insofar as the vascular exchanger functions ideally and osmolalities in DHL, CD, and vasa recta are the same and thus, all approximately equal to that of plasma; the fluid returned by the core to the systemic circulation is isosmolar with plasma and *overall the medulla functions as a segment of proximal tubule.* With nonideal function the medulla returns a slightly hyperosmotic fluid to the systemic circulation. The degree of hypertonicity depends on the efficiency of the exchanger. This relation will be explored quantitatively in a later paper. It is, however, approximately true that the excess water or solute in the final urine equals the solute or water removed by the distal tubule. It might be noted that at least superficially the central core is the macroscopic analogue of the microscopic long pore of the standing gradient theory (Diamond and Bossert, 1967).

The wide range over which the central core model can vary in its mode of operation is possibly its most striking feature. Here, this emerges in the fact that the system can concentrate with a recycling fraction ranging from 1 to 0. It seems plausible that the recycling fraction may vary among species and even in the same individual under different physiological stresses. This variation in mode of operation of the central core model appears to be important both as an adaptive and as a regulatory mechanism.

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