# Isotonic Water Transport in Secretory Epithelia[1,2]

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The model proposed by Diamond and Bossert [1] for isotonic water transport has received wide acceptance in recent years. It assumes that the local driving force for water transport is a standing osmotic gradient produced in the lateral intercellular spaces of the epithelial cell layer by active solute transport. While this model is based on work done in absorptive epithelia where the closed to open direction of the lateral space and the direction of net transport are the same, it has been proposed that the lateral spaces could also serve as the site of the local osmotic gradients for water transport in secretory epithelia, where the closed to open direction of the lateral space and net transport are opposed, by actively transporting solute out of the space rather than into it. Operation in the backward direction, however, requires a lower than ambient hydrostatic pressure within the lateral space which would seem more likely to cause the space to collapse with loss of function. On the other hand, most secretory epithelia are characterized by transport into a restricted ductal system which is similar to the lateral intercellular space in the absorptive epithelia in that its closed to open direction is the same as that of net transport. *In vitro* micropuncture studies on the exocrine pancreas of the rabbit indicate the presence of a small but statistically significant increase in juice osmolality, 6 mOsm/kg $H_2O$, at the site of electrolyte and water secretion in the smallest extralobular ducts with secretin stimulation which suggests that the ductal system in the secretory epithelia rather than the lateral intercellular space is the site of the local osmotic gradients responsible for isotonic water transport.

One of the characteristic features of many of the secretory and absorptive epithelia is isotonic water transport, the transepithelial movement of water in the absence of any overall hydrostatic or osmotic pressure driving force. Since it has been demonstrated in many epithelia that water transport is a passive process dependent on coupling to active solute transport, it is thought that the hydrostatic and osmotic pressure gradients responsible for water movement are produced by active solute transport within the epithelium itself. One mechanism proposed by Diamond and Bossert [1] for isotonic water transport which has received wide acceptance in recent years assumes that these local gradients are produced within the lateral intercellular spaces of the transporting epithelial cell layer.

Our present understanding of the mechanisms responsible for isotonic water transport is based largely on studies done with absorptive epithelia such as the work of Diamond and his colleagues with the gall bladder. In part, this reflects the fact that our knowledge of electrolyte transport mechanisms in the secretory epithelia, in general, has lagged behind that in the absorptive epithelia. Thus, more attention has been focused on electrolyte transport in the secretory epithelia than on water transport. There has been a tendency by some to look upon secretory epithelia as absorptive epithelia functioning in the opposite direction. This concept has even been extended to the mechanism of isotonic water transport in the suggestion by Diamond



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and Bossert [1] that the lateral spaces can function in either direction, thus producing isotonic water transport in both secretory and absorptive epithelia.

In this paper, the applicability of the Diamond-Bossert model and, in particular, the role of the lateral intercellular spaces in the process of isotonic secretion will be reassessed. Analysis of the qualitative features of the Diamond-Bossert model suggests that it is very unlikely that the lateral spaces could function in the backwards direction as would be required for the secretory epithelia. Preliminary evidence from the pancreas, on the other hand, suggests that the local driving forces for water movement may reside within the network of small ducts into which secretion occurs.

## DIAMOND-BOSSERT MODEL

The lateral intercellular spaces are the long narrow channels between adjacent epithelial cells and are bounded on the lumenal end of the cell by the tight junction and on the basal end by the basement membrane. The initial proposal that the lateral spaces were the site of local osmotic gradients was based on microscopy studies of Tormey and Diamond [2] in the gall bladder of the rabbit. They found a relationship between the rate of fluid absorption in the gall bladder and the width of these spaces with the space width increasing as the absorption rate increases. The essential features of the Diamond-Bossert model are outlined in Fig. 1. As viewed in the electron microscope the tight junction is a region where the outer dense lines of the adjacent plasma membranes appear to fuse. Because of this close apposition of the membranes at the tight junction, Diamond and Bossert assumed for calculational purposes that the junctional complex was completely impermeable to both solutes and water. The basement membrane, on the other hand, was assumed to behave as a completely non-selective membrane offering the same resistance to either convection or diffusion as bulk water. Thus the lateral spaces in the gall bladder appear as long narrow channels closed at the lumenal end and open at the basal end. Moreover, the closed to open direction of these channels is the same as the direction of net solute and water transport.

The mechanism by which these lateral spaces function can be visualized as follows. Solute is actively transported from the lumen into a region near the closed end of the space. The resulting high solute concentration at the top of the channel then draws in water by osmosis. The influx of water in turn increases the local hydrostatic pressure within the space which, because of the assumed impermeability of the tight junction, sets up bulk fluid flow toward the open end of the channel. The composition of the final absorbate will be that of the fluid emerging from the channel at the basement membrane and it may vary from isotonic (i.e., in osmotic equilibrium with the lumenal fluid) to hypertonic depending on the model parameters: solute transport rate, water permeability, length of the region for active solute transport and channel dimensions. An essential requirement of the Diamond-Bossert model for isotonic water movement, however, is that active solute transport must be restricted to only a portion of the entire channel length near the closed end.

The major features of the Diamond-Bossert model for isotonic water movement are thus: (i) that the closed to open direction of the lateral intercellular space is the same as the direction of net transport; (ii) that the tight junction is completely impermeable to both solutes and water; and (iii) that active solute transport is restricted to the upper portion of the channel. While direct experimental verification of the details of the Diamond-Bossert model is still lacking, evidence indicates that the lateral spaces play an important role in fluid absorption. For example, the relationship between the width of the lateral spaces and the rate of fluid absorption in

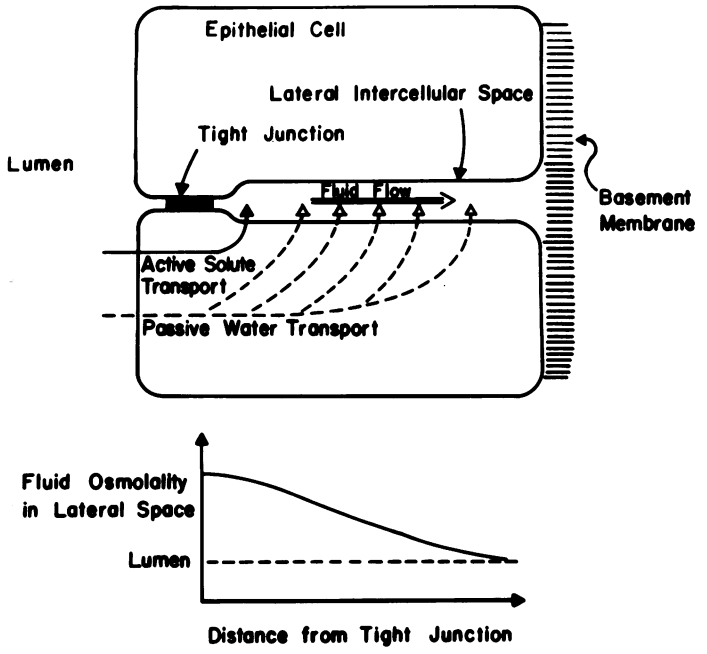


FIG. 1. Schematic representation of the Diamond-Bossert model for isotonic water transport in absorptive epithelia. Active solute transport is restricted to a region near the tight junction while passive water transport occurs along the entire length of the lateral space. Profile of fluid osmolality in space is also shown.

the gall bladder, observed by Tormey and Diamond [2], is what would be expected on the basis of the Diamond-Bossert model. The distention of the lateral spaces at high absorption rates likely results from the higher hydrostatic pressure required to produce the attendant higher bulk fluid flow rates within the space. Direct implication of the lateral spaces in fluid absorption has also been demonstrated in one system, the rectal pad of the insect *Periplaneta.* Wall *et al.* [3] have found that the osmolality of the fluid within the intercellular space was up to 300 mOsm/kg $H_2O$ greater than that of the fluid in the rectal lumen.

## APPLICABILITY TO THE SECRETORY EPITHELIA

While the evidence supports the role of the lateral intercellular spaces in fluid absorption, structural and physiological differences between the secretory and absorptive epithelia make it questionable whether the lateral spaces can serve as the site of the local osmotic gradients for water movement in the secretory epithelia. The tight junctions are located near the lumenal surface of the cell in both secretory and absorptive epithelia. For example, the tight junctions are located at the ductal face in the exocrine pancreas and adjacent to the bile canaliculi in the liver [4]. Since net transport is from blood to lumen in these secretory epithelia, the closed to open direction of the lateral intercellular space and net transport are now opposed.

Diamond and Bossert [1] have proposed that the lateral spaces could function in the opposite direction, with the closed to open direction of the space and net transport opposed, by actively transporting solute out of the space rather than into it. Reversing the direction of active solute transport would lead to low osmotic concentrations within the space, osmotic water fluxes out of the space across the lateral membrane, and bulk fluid movement into the space from the open end. Examination of the Diamond-Bossert model, however, indicates that merely reversing the sign of

solute transport will not transform a system for isotonic absorption into one for isotonic secretion. For example, isotonic absorption requires that active solute transport be restricted to the closed end of the space while osmotic water transport occurs over nearly the entire channel length. In the absorptive epithelia, the high solute concentration at the site of active solute transport is propagated down the channel by both diffusion and convective flow thus ensuring a downstream area for osmotic equilibration. On the other hand, if active solute transport is still restricted to the closed end in the secretory epithelia when the lateral space functions in the opposite direction, convective flow into the space from the open end now opposes the generation of a difference in transmembrane potential along the axis of the channel. Because significant solute concentration differences outside the restricted region of active solute transport could only be obtained by axial diffusion, one would expect a progressively more hypertonic secretion at higher secretion rates as the increased convective flow up the space reduces the effects of axial diffusion and thereby reduces the difference between the areas for water and solute transport. Restricting active solute transport to the basal end of the lateral space would eliminate this problem and favor the production of an isotonic secretion. However, it is not clear that the analysis of the concentration profile within the lateral space alone will provide an adequate description of the composition and rate of the final secretion. The Diamond-Bossert model involves the properties of only a single membrane, the lateral membrane. For absorptive epithelia, once solute and water transport occur across the lateral membrane into the lateral space no further permeability barrier is encountered and thus the composition and the rate of production of the final absorbate is determined by the composition and the velocity of the fluid leaving the lateral space at the basal end. In contrast, for secretion there is no point within the lateral space where the composition of the fluid corresponds to that of the final secretion. Moreover, since the fluid in the lateral space still faces transport across the lumenal as well as the lateral membrane, the composition and rate of secretion will depend on the properties of both membranes and may not be equal simply to the integral of the solute and water transport rates over the length of the lateral membrane.

While these arguments suggest that the Diamond-Bossert model may not be adequate to describe the operation of the lateral spaces in the opposite direction for secretion, further examination of their model argues that the lateral spaces cannot function in the backwards fashion. Convective flow within the lateral space is the result of hydrostatic pressure gradients. For absorption, the hydrostatic pressure at the closed end is greater than that at the basal end and it must increase as the absorption rate increases in order to maintain a steady state between the rate of fluid movement out of the space at the basal end and the rate of solute and water transport into the space across the lateral membrane. In fact, it was the apparent manifestation of this hydrostatic pressure variation as a relationship between the width of the lateral space and the absorption rate in the gall bladder [2] which led to the formulation of the Diamond-Bossert model. In contrast, for secretion the hydrostatic pressure at the closed end of the lateral space must be less than that at the open end in order to obtain bulk fluid movement into the space from the open end and it must decrease as the secretion rate increases. Since the evidence above indicates that plasma membranes are not rigid structures, a lower than local cellular hydrostatic pressure within the lateral space should cause the space width to decrease. However, a decrease in space width would require a further decrease in the local hydrostatic pressure within the space in order to maintain a steady state rate of fluid movement

into the narrower space which would, in turn, further reduce the space width. Thus it seems much more likely that a lower than intracellular hydrostatic pressure within the lateral space would ultimately cause the space to collapse with loss of function rather than to produce fluid movement into the space.

If the lateral spaces do not play a role in the production of isotonic secretions as these arguments suggest, where are the local osmotic gradients which bring about water movement? In most of the secretory epithelia, secretion occurs into a network of small ducts or tubules within the gland. The closed to open direction of these ductal systems is parallel to the direction of net transport and hence they could function in the same manner as the lateral spaces in the absorptive epithelia to bring about isotonic water movement in the secretory epithelia. Consider, for example, the secretory epithelia of the gastrointestinal system: the liver, the exocrine pancreas, and the stomach, all of which produce isotonic secretions. In the liver and pancreas, bile and pancreatic juice are secreted into highly branched tubular systems, the bile canaliculi and the pancreatic ductal system, which permeate the entire glands. Even in the stomach which has the flat sheet structure more characteristic of the absorptive epithelia, acid secretion occurs into the intracellular canaliculi which permeate the individual parietal cells. Moreover, transport studies have generally involved analysis of the fluid after it has left the ductal system rather than the fluid within the ductal system itself so that the possibility that the ductal system could serve as the site of local osmotic gradients remains largely unexplored.

## EVIDENCE FOR OSMOTIC GRADIENTS IN THE PANCREATIC DUCTAL SYSTEM

Within the last few years, information has been obtained on the composition of the fluid within the ductal system of the pancreas through the application of micropuncture techniques. While attention has been focused primarily on the mechanisms of electrolyte rather than water transport, we have examined the osmotic concentration profile within the pancreatic ductal system in the course of our micropuncture studies and our results suggest that the ductal system may indeed serve as the site of osmotic equilibration.

The rabbit pancreas has been most widely used for micropuncture studies because it is a diffuse preparation with most of the ductal system readily accessible for micropuncture. A portion of the rabbit pancreas is shown schematically in Fig. 2. Lobules of primarily protein secreting acinar cells are widely dispersed throughout the connective tissue of the first duodenal loop, the so-called mesomental loop. These lobules are connected, by a network of small ducts 40–200$\mu$ in diameter, to a single main collecting duct which enters the intestine apart from the common bile duct. This portion of the ductal system will be referred to as the extralobular ducts. Within the lobules, the ductal system extends from a single duct confluent with the extralobular system to the blind ending acini which are a few microns in diameter and are lined by the acinar cells. This portion of the ductal system will be referred to as the intralobular ducts.

In most species, pancreatic electrolyte secretion is under the control of the hormone secretin. In the rabbit, however, secretion occurs even in the absence of hormonal stimulation [5]. Because of the diffuse nature of the rabbit pancreas, it can be maintained in a saline environment gassed with 95% $O_2$ – 5% $CO_2$ and will continue to secrete *in vitro* in the absence of exogenous secretin for many hours at a rate that is comparable to that observed *in vivo* in the absence of the hormone [6]. We

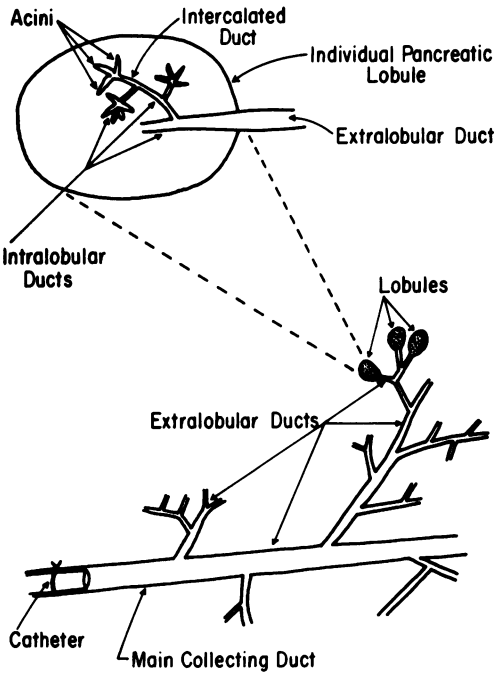


FIG. 2. Schematic representation of rabbit pancreas.

chose to carry out our micropuncture studies using the *in vitro* preparation. Because our primary objective was to study the mechanism of electrolyte secretion, the ability to widely vary and maintain close control over environmental conditions *in vitro* provided distinct advantages for such a study. However, as will be seen, the *in vitro* preparation poses problems in studying the mechanisms of water transport.

Our micropuncture studies indicate that secretion occurs by the whole tissue mechanism shown schematically in Fig. 3 [7]. This mechanism was determined primarily by analysis of concentration profiles of the secreted ions and proteins within the ductal system. The latter was of particular importance because the digestive proteins are secreted by the acinar cells which line the most proximal portion of the ductal system. Any change in protein concentration distal to the acini must reflect a site of electrolyte and water secretion. In the absence of secretin stimulation, spontaneous secretion occurs within the intralobular ducts. The extralobular ducts behave as a passive conduit except for the main collecting duct where $Cl\text{-}HCO_3$ exchange occurs in the absence of net fluid movement. With secretin stimulation, secretion occurs within the smaller extralobular ducts as well as in the intralobular ducts. The main collecting duct, however, has no secretory capacity even in the presence of the hormone, performing only $Cl\text{-}HCO_3$ exchange.

The whole tissue mechanism of electrolyte secretion in the rabbit pancreas bears strong resemblance in its overall organization to the Diamond-Bossert model for isotonic water movement. The pancreatic ductal system is a long narrow channel with its closed to open direction parallel to that of net transport. Active solute transport is restricted to a region near the closed end and osmotic equilibration could be obtained in the distal segment where no net solute transport occurs. Thus, the ductal system in this secretory epithelium could function to bring about isotonic water transport in a manner analogous to that proposed by Diamond and Bossert for the lateral intercellular spaces in absorptive epithelia.

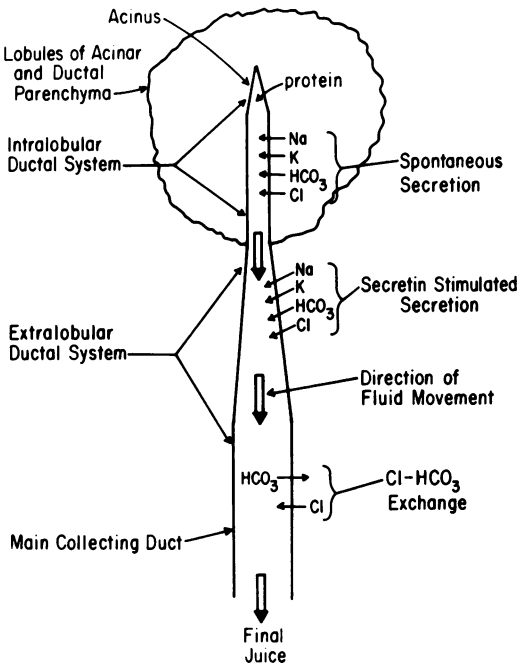


FIG. 3. Schematic representation of organization of electrolyte secretion at the whole tissue level in the rabbit pancreas. The separation of spontaneous electrolyte and protein secretion in the intralobular ducts indicates functionally distinct and not necessarily spatially distinct processes.

Case *et al.* [8] have shown using the vascularly perfused cat pancreas that the juice leaving the gland is always in osmotic equilibrium with its environment even when the perfusate osmolality was varied over a range of 100–500 mOsm/kg $H_2O$ by varying its NaCl concentration. We have obtained similar results using the *in vitro* rabbit pancreas [9] and these results are analogous to those obtained by Diamond for absorption in the rabbit gall bladder [10]. If the ductal system of the pancreas functions in the same manner as the lateral spaces in absorptive epithelia, significant increases in juice osmolality should be found in the ductal system at the sites of secretion: within the intralobular ducts during spontaneous secretion and in the smaller extralobular ducts as well during secretin stimulation.

While the *in vitro* preparation offers distinct advantages for studying electrolyte transport, its utility for studying water transport is limited. Samples of juice have been obtained from the smallest intralobular ducts *in vivo,* but for technical reasons *in vitro* micropuncture is limited to the extralobular ducts. Thus using the *in vitro* preparation, juice osmolality at the site of secretion can be determined only for secretin stimulated secretion. Fig. 4 presents the osmolality and Cl concentration profile within the extralobular ducts for typical experiments during spontaneous and secretin stimulated secretion (GIH Research Unit, Karolinska Institut, Stockholm). Duct diameter increases continuously in the direction of fluid movement and is used as a qualitative measure of position within the intralobular ducts. For spontaneous secretion which is produced within the intralobular ducts, juice osmolality is constant from the smallest extralobular ducts to the final juice and is in equilibrium with that of the *in vitro* bathing solution. Cl concentration in the micropuncture samples of ductal juice is essentially constant but less than that in the final juice which reflects the presence of Cl-$HCO_3$ exchange in the main collecting duct. With secretin stimulation

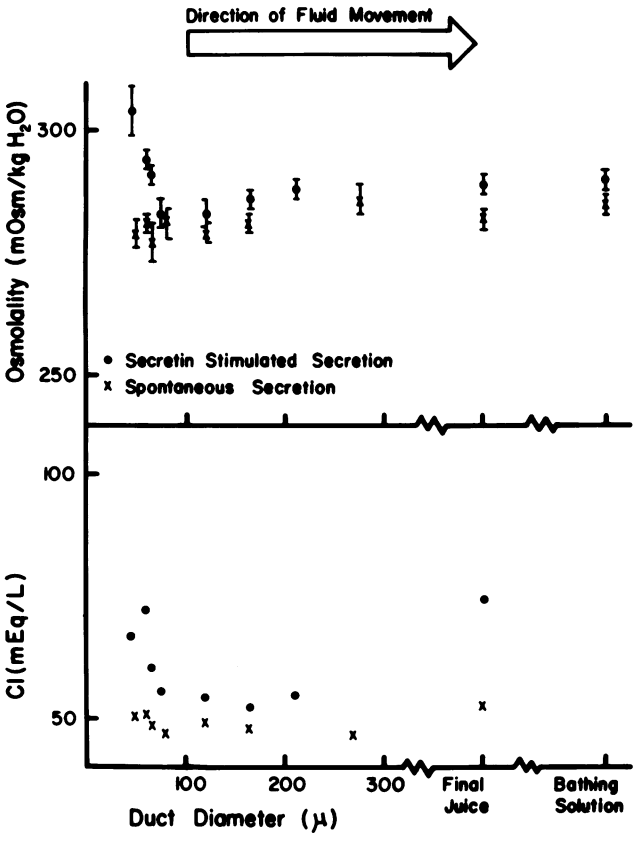


FIG. 4. Osmolality and Cl concentration profiles in the extralobular ducts for typical experiments during spontaneous and secretin stimulated secretion. Osmolality of final pancreatic juice and the *in vitro* bathing solution are shown at the right. Bars on the osmolality data represent experimental error in analysis. Experimental error in Cl analysis is not shown but in all cases is ± 1 mEq/L or less. Increases in both juice osmolality and Cl concentration are present at the site of electrolyte and water secretion in the smallest extralobular ducts with secretin stimulation.

a marked increase in juice osmolality is observed in the smallest extralobular ducts of 40–70$\mu$ in diameter while in the larger ducts juice osmolality again is constant and in equilibrium with the bathing solution. The secretin stimulated extralobular secretion has a higher $HCO_3$, and a lower Cl, content than that of the intralobular secretion [7,11] and the marked decrease in Cl concentration in the direction of fluid movement in the smallest extralobular ducts indicates that the increase in juice osmolality occurs at the site of the extralobular secretion. The subsequent marked increase in Cl concentration from the largest duct punctured to the final juice again reflects Cl-$HCO_3$ exchange in the main collecting duct. The significance of this osmotic increase observed in the presence of secretin can be seen in Table 1 which presents the average juice osmolality and electrolyte composition in the small ($<70\mu$ in diameter) and large ($>70\mu$ in diameter) extralobular ducts for several experiments with and without secretin stimulation. For spontaneous secretion, there is no significant difference ($P > 0.6$) between the osmolality in the small and large extralobular ducts. With secretin stimulation, however, the osmolality in the small extralobular ducts averages 6 mOsm/kg $H_2O$ greater than that in the large extralobular ducts. This difference is statistically significant ($P < 0.005$) as is the difference between the osmolality in the small extralobular ducts with secretin and that in both the large and small extralobular ducts during spontaneous secretion ($P < 0.001$).

TABLE 1
Osmotic and Ionic Concentrations in the Extralobular Ducts[a]

| | Extralobular Ducts | |
|---|---|---|
| | > 70 μ Diameter | < 70 μ Diameter |
| Spontaneous Secretion | | |
| Osmolality (mOsm/kg $H_2O$) | 284 ± 6 (14) | 283 ± 4 (10) |
| Na (mEq/L) | 152 ± 2 (14) | 153 ± 2 (10) |
| K (mEq/L) | 6.5 ± 0.4 (14) | 6.5 ± 0.2 (10) |
| Cl (mEq/L) | 57 ± 8 (14) | 58 ± 7 (10) |
| $HCO_3$ (mEq/L) | 101 ± 8 (14) | 102 ± 6 (10) |
| Secretin Stimulated Secretion | | |
| Osmolality (mOsm/kg $H_2O$) | 286 ± 6 (22) | 292 ± 6[b] (18) |
| Na (mEq/L) | 153 ± 4 (18) | 155 ± 4 (12) |
| K (mEq/L) | 6.9 ± 0.4 (18) | 6.9 ± 0.4 (12) |
| Cl (mEq/L) | 64 ± 8 (22) | 75 ± 9 (18) |
| $HCO_3$ (mEq/L) | 97 ± 9 (22) | 86 ± 9 (18) |

[a]The data from four experiments during spontaneous secretion and seven experiments with secretin stimulation are presented ± 1 SD. The number of individual micropuncture samples is indicated in parentheses. Secretin concentration in the *in vitro* bathing solution was 215 or 430 U/L.

[b]Osmolality in the small extralobular ducts with secretin stimulation is significantly different from that in the large ducts with secretin ($P < 0.005$) and from that in both the small and large ducts during spontaneous secretion ($P < 0.001$). Osmolality in the large ducts with secretin is not significantly different from that for spontaneous secretion ($P > 0.2$).

The significant increase in juice osmolality at the site of secretion in the presence of secretin stimulation supports the ductal system as the site of the local driving force for water movement. However, the magnitude of this increase, averaging 6 mOsm/kg $H_2O$, is substantially below the 50 mOsm/kg $H_2O$ or more increase calculated by Diamond and Bossert [1] for the top of the channel or the up to 300 mOsm/kg $H_2O$ increase observed in the lateral space of the rectal pads of *Periplaneta* by Wall *et al.* [3]. There are several possible explanations for this difference. First, the permeability properties of the exocrine pancreas are not known and may be different from those in *Periplaneta* and those used by Diamond and Bossert in their model calculations. Second, the increase calculated here is the average over the 40 to 70μ duct diameter range and larger increases may be present in the most proximal portion of the extralobular ducts and in the intralobular ducts as well. For example, the data in Fig. 4 suggest that the osmotic increase in the smallest extralobular ducts (those less than 50μ in diameter) may be 10–15 mOsm/kg $H_2O$, which is in reasonable agreement with the indirect estimate based on diffusion potential measurements by Machen and Diamond [12] of 20 mOsm/kg $H_2O$ for the lateral space of the rabbit gall bladder. Third, for reasons which are not known, the stimulation in secretion rate produced by secretin *in vitro* is much less than that observed *in vivo* [6,7], even though the composition of the extralobular secretion both *in vitro* and *in vivo* are comparable [7, 11]. Larger osmotic increases may be produced at the greater secretin stimulated secretion rates *in vivo*. This latter possibility, however, seems unlikely. While previous *in vivo* micropuncture studies in the rabbit pancreas have not been analyzed for juice osmolality, some indirect information on juice osmolality can be obtained from the juice cation concentration measurements of Mangos and McSherry [13]. Juice osmolality is almost entirely accounted for by the major electrolytes (Na, K, Cl and $HCO_3$). Because Na is the predominant cation (150–155 mEq/L versus 5–7 mEq/L for K) [6,7,13], any change in juice osmolality should be reflected in a proportional change in juice Na concentration. The data in Table 1 indicate a 2 mEq/L difference in juice Na concentration between the small and large extralobular ducts with

secretin which agrees well with the 3 mEq/L difference expected on the basis of the 6 mOsm/kg $H_2O$ difference in osmolality. This Na concentration difference, however, is not statistically significant ($P > 0.2$), primarily because of lack of sufficient sensitivity in the ultramicro cation analysis. No marked differences are apparent between the Na and K concentration of the intralobular and final juice in the *in vivo* data of Mangos and McSherry [13] which suggests that any osmotic increase *in vivo* is unlikely to be greater than 10–15 mOsm/kg $H_2O$. The only osmolality measurements of intralobular juice come from *in vivo* micropuncture studies on the pancreas of the mouse by Mangos *et al.* [14]. They report that in the presence of secretin stimulation the osmolality of the fluid in the acini is about 10 mOsm/kg $H_2O$ above plasma levels and above that in the acini in the absence of secretin. The magnitude of this osmotic increase agrees with that reported here and provides further support for the presence of local osmotic gradients in the ductal system of the pancreas.

Because of the small magnitude of the osmotic increase with secretin and the limited data available, it is not possible to correlate quantitatively the length of the region of increased osmolality with that for active solute transport. However, the apparent correspondence between the regions of increased osmolality and Cl concentration in Fig. 4 suggests that these two are unlikely to be markedly different. This appears to contradict one of the requirements of the Diamond-Bossert model, that the region for osmotic equilibration exceeds that for active solute transport. One might also have anticipated some hypertonicity in the fluid leaving the intralobular ducts during spontaneous secretion on the basis of the Diamond-Bossert model whereas the data indicate that the juice is osmotically equilibrated by the time it reaches the extralobular ducts. In a previous paper in this Symposium, however, Boulpaep and Sackin [15] have shown that the requirement that active solute transport be restricted to a region near the top of the channel can be eliminated by dropping the assumption that the tight junction is impermeable to solutes and water. While the geometry of the pancreatic ductal system differs from that of the lateral space in that many tight junctions are located along the length of the channel instead of a single tight junction at the top of the channel, the net result of a leaky tight junction is likely to be the same: to accelerate osmotic equilibration by increasing the effective water permeability and by allowing for the passive back diffusion of solute. Interestingly, Boulpaep and Sackin [15] have also found that the maximum osmotic increase in the channel is markedly reduced by making the tight junction leaky which might explain the relatively small magnitude of the osmotic increase observed in the pancreatic ductal system.

Although these data are preliminary and not fully conclusive, they do support the present contention that the ductal system in the secretory epithelia rather than the lateral intercellular spaces is the site of the local osmotic gradients responsible for isotonic water transport. Further investigation is clearly warranted. The rabbit pancreas offers an ideal preparation for such investigation because the whole tissue mechanism of secretion is reasonably well understood and samples of juice from the entire ductal system can be obtained using *in vivo* micropuncture techniques. If local osmotic gradients are located within the ductal system, such study would add immeasurably to our understanding of the mechanism of isotonic water transport since it would provide a system which is amenable to direct experimental analysis. Not only can the osmolality profile over the entire length of the ductal system be determined but also the active solute fluxes and water permeability can be measured using split drop microperfusion techniques for use in appropriate mathematical models such as those developed by Diamond and Bossert or Boulpaep and Sackin.

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