into vesicular lipid bilayers. Further purification will then make it possible to obtain information on the molecular structure of the active sites of the transport system and of the sites where regulation of the activity takes place.

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Physiological Consequences of the Cellular Distribution of Sodium-plus-Potassium Ion-Dependent Adenosine Triphosphatase

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The tubular epithelium of the mammalian kidney belongs to a general class of tissues that are known collectively as transporting epithelia (Berridge & Oschman, 1972) and that are universally distributed among the coelomate metazoans. Almost exclusively, these cellular monolayers or cornified multilayers lie on the boundary between the interior of the organism and the environment. They are, however, often removed from direct contact with the exterior by systems of ducts and sphincters. As a consequence of their location, transporting epithelia are the mediators of solute exchange between the organism and its environment and are responsible for the homoeostasis of the interior. It shall be argued that these tissues carry out their diverse functions by relying upon an invariant fundamental pattern of organization. To understand the behaviour of renal tubular epithelia, these rules governing the performance of all transporting epithelia must be thoroughly grasped.

From an examination of the ultrastructure of a large number of transporting epithelia (Berridge & Oschman, 1972), it can be concluded that they are all constructed with an identical morphology (Bulger, 1965). The plasma membrane of every cell is subdivided, by the continuous ring of the tight junction, into a luminal surface in direct contact with the environment and a basolateral surface. The distribution of membrane-bound enzymes (Kyte, 1976a) and other macromolecules (Miller & Revel, 1975) displays an abrupt discontinuity at the tight junction. This observation suggests that this organelle is a boundary through which lateral diffusion cannot occur. Above and below this ring of containment, however, macromolecules appear to be distributed uniformly over the plasma membrane (Kyte, 1976b) and other macromolecules (Miller & Revel, 1975) displays an abrupt discontinuity at the tight junction. This observation suggests that this organelle is a boundary through which lateral diffusion cannot occur. Above and below this ring of containment, however, macromolecules appear to be distributed uniformly over the plasma membrane (Kyte, 1976a,b). The tight junction is also responsible for joining the cells together in a continuous sheet. The outermost permeability barrier thus becomes an unbroken surface composed of the luminal portions of the cell membranes, the tiles, and the tight junction, the grout. Below the tight junction lie the intercellular spaces. All of the narrow membrane-limited extracellular spaces observed within the epithelia lie between separate cells and are, as a result, directly connected with the tight junction. The contraluminal surfaces are in direct contact with a basement membrane whose permeability properties are poorly understood. A diagrammatic representation of the general morphology of transporting epithelia is presented in Fig. 1.

Without exception, it has been observed that the net flux of all solutes and solvent against their concentration gradients across transporting epithelia are eliminated by the addition of a cardiac glycoside. These ligands are highly specific inhibitors of (Na⁺+K⁺)-
dependent adenosine triphosphatase, the enzyme whose only catalytic reaction is represented by the following equation (Goldin, 1977): 

\[ 3Na^+_{i} + 2K^+_{o} + MgATP \leftrightarrow 3Na^+_{o} + 2K^+_{i} + MgADP + P_i \]

where \(i\) and \(o\) refer to the inside and outside of the cell respectively. With only one exception (Quinton et al., 1973), it has been shown that this membrane-bound enzyme is concentrated in the basolateral surfaces of the epithelial cells (Schmidt & Dubach, 1971; Heidrich et al., 1972) and is thickly and uniformly distributed over this surface (Ernst, 1972; Kyte, 1976a,b). In general, most of the basolateral surface is adjacent to intercellular space and mitochondria are found in large numbers lining the membranes which define this space. It can be concluded that the mitochondria generate ATP which is almost exclusively consumed by the neighboring \((Na^++K^+)-dependent adenosine triphosphatase which in turn transports vast quantities of Na\(^+\) into the intercellular spaces (Diamond & Bossert, 1967). In fact it has been calculated that the rate at which the mitochondria can provide MgATP may be the rate-limiting step in the sequence (Kyte, 1976b). The high permeability of the basolateral membrane to K\(^+\) (Giebisch et al., 1966; Sullivan, 1968) permits this cation to recycle continuously from cell to intercellular space to support the fluxes of Na\(^+\) (Podevin & Boumendil-Podevin, 1972). The epithelial cell maintains a stable ionic composition, high in K\(^+\) and low in Na\(^+\) (Peaker, 1971), even though considerable fluxes of Na\(^+\) are passing through it. As a result, there is always a Na\(^+\) concentration gradient into the cell from all sides down which Na\(^+\) passively flows through various transport proteins. From within the intercellular space, Na\(^+\) can leave profitably only through the basement membrane into the interior of the organism or through the tight junction into the environment. It is firmly established that many tight junctions show significant permeability to Na\(^+\) (Diamond, 1974). A diagrammatic summary of the various Na\(^+\) fluxes constructed from these considerations is presented in Fig. 2.

The remainder of the net fluxes across the epithelium simply respond to the underlying Na\(^+\) flux. Fluid flux is osmotic and relies on the water permeability of the epithelium (Wright et al., 1972). Sugar and amino acid flux follow a coupled transport process (Schultz & Zalusky, 1964). It has recently been shown that even Cl\(^-\) has a Na\(^+\) coupled carrier that permits its net flux to occur against a concentration gradient across the epithelium (Frizzell et al., 1975).

So far, a general scheme for the organization of transporting epithelia has been described. It is within this basic framework that evolution has operated to create the peculiar capacities of the individual tissues. There are several properties that have been controlled by the process of natural selection. These are the water permeability of the
epithelium, the ionic permeability of the tight junction, the types of coupled transport proteins that have been inserted into the luminal surface, the number of mitochondria provided, the amount of luminal, intercellular and contraluminal surface area and the actual concentrations of each transport protein within the various surfaces. Two amusing examples of this modulation will be discussed.

The avian salt gland is perhaps the most irregular transporting epithelium. It is capable of creating an efflux of 1 M-NaCl from the organism (Schmidt-Nielsen, 1963) drawn from an iso-osmotic plasma. Only a few adjustments of the basic epithelial organization are required to explain this secretion (Kyte, 1976b). The permeability of the epithelium to water is adjusted to a low value. The luminal surface of the cell is made impermeable to everything. The surface area of the intercellular space is enormously expanded and filled with (Na++K+)-dependent adenosine triphosphatase. Large concentrations of mitochondria are provided. The tight junction is made highly permeable. Na+ and Cl− are allowed to enter the contraluminal surface of the cell. As a result of these reasonable changes, highly concentrated NaCl solution accumulates in the intercellular space. A portion of the NaCl in this solution must exit the intercellular space through the tight junction and water enters the intercellular space through the tight junction. Nothing flows across the luminal plasma membrane. Many morphological and histochemical observations are consistent with this proposal (Ernst, 1972).

The mammalian intestine, when exposed to cholera toxin, ceases to absorb iso-osmotic fluid and instead secretes iso-osmotic fluid. It has been demonstrated that the coupled transport of Na+ and Cl− across the luminal surface of the epithelial cell, which normally accounts for approx. 20% of the unidirectional influx of the Na+, is eliminated when the cell is treated with toxin (Nellans et al., 1973). This is the only permeability change in the epithelium which has been observed so far. The permeability of the intestinal epithelium to water is presumably so great that fluid flux can be equated with solute flux. The principal solute fluxes are those of Na+ and its counterions Cl− and HCO3−. The net flux of Na+ across the epithelium is necessarily the difference between the net flux of Na+ into the epithelial cell at the luminal surface down its concentration gradient and the net flux of Na+ and its counterions out of the intercellular space through the tight junction which in the intestine is highly permeable to ions (Munck & Schultz, 1974). When the former is decreased by the elimination of the NaCl co-transporter, the secretion, which is always present and unaffected by the toxin treatment, becomes greater than the absorption.

In conclusion, it is proposed that all transporting epithelia must be organized with adherence to a set of rigidly prescribed rules. The invariant principles are luminal—
basolateral segregation, the permeability of the tight junction, basolateral concentration of the (Na\(^+\)+K\(^+\))-dependent adenosine triphosphatase, the Na\(^+\)-enriched intercellular space, the absolute direction of the five net Na\(^+\) fluxes within the tissue, and luminal co-transport. Certainly the adherence of every epithelium to every rule has not been substantiated. Few exceptions, however, to these principles have been observed so far.


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**Intrarenal Action of Angiotensin**

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**Recent Advances in the Study of the Disturbance of Electrolyte Transport in Bartter’s Syndrome**

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**Renal Role of Parathyroid Hormone**

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