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The economy of the columnar epithelial cell

'Entia non sunt multiplicanda sine necessitate' said William of Occam, and it has always been a laudable aim of science to explain experimental findings and observations with the fewest and simplest hypotheses. The intestinal epithelial cell has undoubtedly a multiplicity of functions even if only the absorptive activities are included[1,2,3] and much ingenuity has been used in the past decade to explain how these functions are carried out. The most striking of these activities are the high degree of selectivity the cells exert on what is transferred, the ways in which large hydrophilic molecules pass through a membrane which is at least partly lipid, the electrical phenomena associated with transfer of non-electrolytes and the general problem of how the columnar cell acts as a transducer in converting metabolic energy to osmotic work. Is it possible to find some one basic mechanism which could underlie all these processes and which could be applied to intestinal absorption of chemically unrelated groups of substances? Any attempt to do this is an aim worth pursuing.

It involves first careful thinking about the definition of active transfer by the intestine. A common view is that active transfer is movement of a substance against its electrochemical potential, and substances which do not exhibit this feature are regarded as being transferred passively. Another view is that processes showing 'saturation kinetics' are active, while those showing 'diffusion kinetics' are passive. These views contain some serious fallacies not always appreciated, and these fallacies are of two kinds: (1) failure to recognize an active component which exists, and (2) postulation of an active process which does not exist. The first is more simply dealt with. If an absorption process shows diffusion kinetics, *ie*, the rate of absorption is proportional to concentration, this does not necessarily mean that no active process is involved. It can either mean that the active process is not the rate-limiting stage in a series of processes, or alternatively, the process is functioning very much below its maximum capacity. Furthermore, the fact that a substance moves downhill does not imply that no other driving force is being used. Probably no reader of this article normally relies on the favourable road gradient to propel his car downhill.

The second fallacy, *ie*, unnecessary postulation of an active process, is of a more subtle kind. Let us oversimplify the problem by regarding the intestinal epithelial cell layer as a membrane separating two compartments and able to move substances from one to the other. If we simplify the system still further and consider that only one solute (and no solvent) is being transferred, the concept of active transfer is easy and the work done in transfer can be calculated from the concentration change produced. If we increase the complexity by adding only one additional component, the problem is immediately more difficult. For even if it is found that two substances are moved each against their concentration gradient (assuming no electrical charges or potentials are involved) we cannot say that each involves 'active' transfer, because the concentration change created by the movement of one could provide the energy for movement of the other. In a multicomponent system, and this includes all biological systems, it is not sufficient to say that a substance is 'actively' transferred, but it is necessary to ask whether it is the primary substance involved in active transfer or whether its movement is only secondary to the movement of some other substance. The primary substance is the one whose transfer is coupled, not to the transfer of another substance, but to metabolism. When we appreciate that metabolism itself may be a process of transfer, *eg*, electron transfer, it is evident that semantic and other pitfalls beset enquiring footsteps. Nonetheless there is a useful distinction between transfer coupled to metabolism (primary active transfer) and transfer coupled to transfer of other substances (secondary active transfer). The results of this consideration can be at the same time both depressing and encouraging—depressing because it leaves us less certain whether the systems we are accustomed to call active are really active, encouraging because the possibility is opened up of applying 'Occam's razor', and postulating one primary transfer to which others can be coupled.

Of the various transfer systems in the intestine which have strong claims for consideration as primary systems, *ie*, linked directly to metabolism, the most obvious candidate is the sodium pump. If an electrogenic sodium pump is postulated at the side of the cell remote from the brush border which is able to pump Na ions from the interior of the cell into the subepithelial fluid at the expense of metabolic energy, what other phenomena could be explained by this? The possibilities are impressive—hexose transfer, amino acid transfer, volatile fatty acid transfer, fluid transfer, anion transfer, and electrical potential —and are worth considering.

Hexose transfer could be coupled to movement of Na by the membrane ternary complex.[4, 5] The underlying idea is that there are membrane carriers which are able to transfer substances by offering specific sites for attachment and then, either by diffusion or rotation or some other kind of movement, bringing these sites into alternate contact with the fluid on each side of the membrane. This process is called facilitated diffusion, and the ternary complex involves a carrier with two sites, one for Na and one for hexose. If a gradient is provided for one of the substances the other must move with it since they are linked in the carrier complex. The gradient could be achieved by a Na pump removing Na from the cell, so that the Na pump could provide the energy for movement of hexose against its concentration gradient. In the terminology used here movement of Na would be primary active transfer, *ie*, linked to metabolism, while hexose transfer would be secondary active transfer, *ie*, linked to movement of Na. There are other ways also in which Na and hexose movement could be linked, *eg*, by the concentration of Na affecting the affinity of the carrier for hexose,[6] again a Na pump being the primary agent in hexose transfer. The same principles apply also to transfer of amino acids, and it has been suggested that either a ternary carrier[7] or a process of facilitated diffusion with differential affinity[8] due to concentration of Na might link amino acid transfer with a Na pump.

The coupling between fluid movement and Na seems well established, and has been suggested by various authors.[9,10] Modern views on fluid transfer tend to discount a pure 'water' pump and to consider that water moves as a result of solute movement.[11] If we accept this view then Na and its accompanying anion, which is quantitatively the most important solute, must play a large role. The coupling of anion movement with a Na pump is also easy to visualize, as the electric potential created by the electrogenic Na pump would itself produce an electrical force to move Cl or bicarbonate ions. This has also been considered as a possible factor in the movement of volatile fatty acids.[12] Lastly the electric potential associated with hexose[13] and amino acid movement[14] could be caused by the electrogenic Na pump[5] at the serosal side of the cell, particularly as there is evidence that the potential change occurs across the membrane at the serosal side of the cell.[15,16]

The idea of a sodium pump as the primary activity in the intestinal epithelial cell is undoubtedly an attractive one, but must not prevent us asking the question, How does it fit in with the experimental observations? It certainly does fit in with some of them, although others are more difficult without bending the facts a little to fit the theory. Probably an Na pump is the chief cause of water being moved by the intestine, although it is likely that other solutes absorbed by the intestine can also cause osmotic movement of water.[8,17,18] It may also be premature to dismiss completely the idea of some sort of mechanism in the cell for generating hydrostatic pressure, *eg*, a contractile vesicle, although no evidence for this is available. The movement of anions would seem to be the simplest kind of dependence on a Na pump, but there is in fact some evidence of independent anion pumps—probably for both chloride[10] and bicarbonate.[19] The linking of hexose and amino acids to movement of Na is perhaps the most interesting; and no one yet has suggested a better explanation than the two suggested by Crane and his colleagues.[4,6] However, there are some awkward facts here too. Inhibition of the Na pump might be expected to inhibit movement of both hexose and amino acid. However, in the rat intestine ouabain affects these two substances at different concentrations.[8] Furthermore, if the intestine is short circuited so as to increase movement of Na, movement of hexose is not affected.[17] There are also difficulties about equating Na movement with the short circuit current,[17,20] and there is evidence for other Na pumps not related to the electrical potential.[17,20] All of these considerations cause some reservations about accepting the Na pump as the driving force for other activities, and it is perhaps a little naïve to think of the cell as a bag of fluid containing certain organelles but with the transfer activities restricted to the bounding membranes, the other contents of the bag being used only to supply energy.

The fact is that biological activities are usually not simple processes, and the search for unifying principles can sometimes be misleading, particularly if we look for the wrong unifying principle. The enormous species variation in what are regarded as fundamental processes must make us doubt sometimes whether we have really discovered what the fundamental processes are. The economy of hypothesis required by Occam is only valid if it really explains all the facts, and someone has expressed the matter picturesquely by saying that God does not always shave with Occam's razor. And yet we feel intuitively that there are basic underlying processes. One of the fascinating questions of gastroenterology is whether the Na pump will in fact ultimately turn out to hold the key to so much of what happens in the columnar epithelial cell.

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