(or, in my treatment, separate and then come to relative rest) if their *only* motions are uniform. Dingle's example of the three uniformly moving clocks B, B', and C is not a correct parallel to the journey of the twins; to be correct, one twin would have to transfer from B' to C in passing, and his motion would then not be uniform.

Dingle's other argument, used three times in the above letter, is based on a misuse of the concept of simultaneity. He says: "Nature provides no unique means of synchronizing clocks at different places," and from the context it is clear that he means this to apply to cases in which the clocks are at relative rest. Now there is a perfectly good way (in fact, there are many ways) to synchronize distant clocks fixed in the same inertial system. This fact is, as far as I know, recognized in all the standard works on the subject. Dingle, while refusing to accept a criterion of simultaneity in the only case where it is valid, has used it in the case of clocks with relative motion, where it is not valid, in an earlier paper [*Nature* **179**, 1242 (1957)].

In closing, I would like to say that both Crawford and I feel that we have said all that we usefully can on this subject; if further rejoinders should be made, we would be inclined to leave the privilege of replying to others.

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Transport of Molecules into Cells against a Concentration Gradient

In an excellent review of endocrine control of amino acid transfer, Noall, Riggs, Walker, and Christensen [*Science* **126**, 1002 (1957)] assume an enzymatic process in concentrative transfer across cell barriers, or of transport of molecules into cells against concentration gradients. Is it not pertinent here to suggest the possibility that the process may be pinocytosis, the remarkable phenomenon of "cell drinking" which was first described by Warren Lewis [*Bull. Johns Hopkins Hosp.* **49**, 17 (1931)]? This may be beautifully demonstrated in phase-contrast time-lapse movies, as has been done for so many tissues by many competent cytologists.

The free edges of cells in tissue culture, as recorded by phase-contrast time-lapse movies, are in continual wavelike movement, laving the medium around the cells and often sweeping over and engulfing a portion of the surrounding fluid, forming what is usually called a "vacuole," but which contains the various molecules that may be in the surrounding liquid. This "vacuole" may be seen to move toward the center of the cell, into which it has been swept by the curling edges, and, as it moves, the phase boundary between it and the cyto-

plasm of the cell becomes less and less distinct, until presently there is no "vacuole." Its contents then have been incorporated into the cytoplasm.

Under this interpretation, the action of the hormones cited by Noall and his associates may consist in speeding up the process of pinocytosis, so that the amino acid concentration in cells increases while that of the extracellular fluid decreases. Pinocytosis is applicable of course to many other situations involving "transport against concentration gradients" in regard to cells, or indeed to the entrance of large molecules of any sort into the cytoplasm of cells.

Let us not be misled by the dead appearance of cell boundaries in stained and fixed preparations into thinking *only* and exclusively in terms of a semipermeable membrane and its behavior. In living mammalian cells there is a phase boundary separating the cells from the extracellular fluid around them, and this phase boundary is in continual activity, exhibiting continual pinocytosis. This does not preclude ion passage across the phase boundary, but in the living cell it does suggest the possibility of another mechanism which may be significant when large molecular particles are involved.

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The interest of Leake and Pomerat in the paper of Noall *et al.* is greatly appreciated, as is the opportunity of commenting on their suggestion.

Although "cell-drinking" obviously concentrates no extracellular solutes, conceivably active transport is directed toward the contents of a vacuole rather than toward the whole outside environment. Such a narrowing of transport activity to the interior of the cell seems to us to place a *lower* estimate on the potentialities of the cell boundary. In any event the entire process of *active* transport is still left for explanation; in fact, the difficulties in explaining the rate, specificity, and efficiency of the process appear to be more severe.

If it is by pinocytosis that amino acids are transferred into cells, then the engulfing and dissipation of "vacuoles" must be fast enough to account for the rate of entrance of the amino acids. Our colleague Erich Heinz finds that half the glycine of ascites tumor cells is exchanged with labeled glycine from outside in about 2 minutes [*J. Biol. Chem.* **211**, 781 (1954)]. For this to occur by pinocytosis demands that in this brief interval the cell must engulf a quantity of suspending fluid several times its own volume, since the cellular glycine level is many times the extracellular. In addition, an equivalent amount of solvent molecules must be expelled. Our impression is that a substantial part of the cell glycine may be exchanged while a pinocytotic vacuole hesitates at the cell periphery.

A better assessment of the part played by pinocytosis in amino acid uptake comes from the relationship between glycine *influx* and the external glycine *level*, shown in the same investigation. As the glycine level is raised, the engulfed vacuoles will be correspondingly richer in glycine and the initial rate of entrance should rise. In actual fact, as the glycine level was raised the influx soon reached a maximum rate, which then remained constant over a considerable range of glycine levels. It is hard to see how the amount of glycine engulfed pinocytotically could be independent of the external glycine level.

At least in the case of the Ehrlich cells, such results do not appear compatible with a large participation by pinocytosis.

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