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To what extent can these various aspects of cell motility be integrated into an exploitable concept, particularly with regard to cell locomotion? In the following contribution, the two basic elements of such a concept—the generation of motive force and the latter's transformation to locomotion—are evaluated.

Conformance Versus Divergence: A General Consideration

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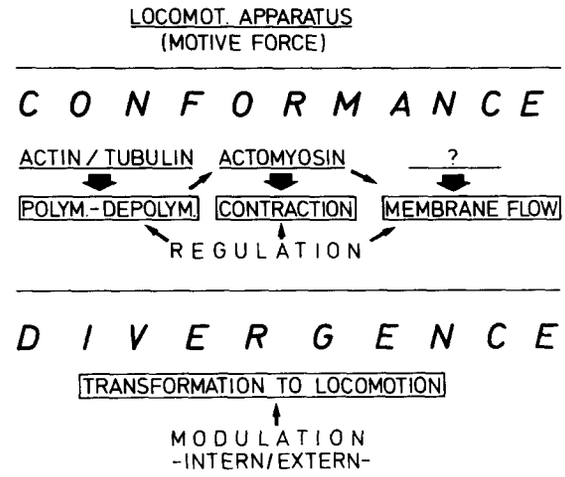
FOR THE initiation and maintenance of cell locomotion, two main prerequisites must be fulfilled: a motive force must be generated and this force must be transformed to actual translocation of the cell. During the last decade, chemo-mechanical energy transformation in unicellular organisms and in tissue cells has been associated with two protein systems: the cytoplasmic actomyosins and the tubulin–dynein system. While it is an established fact that actomyosin plays a major role in motive force generation, the extent to which cytoplasmic microtubules participate in this step is still unclear. Polymerization processes have been considered, especially since it was shown that cytoplasmic actin can produce motive force by undergoing polymerization without involvement of an ATP-ase. In addition to polymerization $\leftrightharpoons$ depolymerization and to contraction, it cannot be ruled out that membrane movement phenomena (membrane flow) also contribute to locomotion by means of unknown force-developing processes within the membrane itself.

In the following diagram, the mechanisms definitely or possibly involved in the generation of motive force are presented.

The diagram emphasizes the concept that on the molecular level of motive force generation, there exists a certain *Conformance* of phenomena, while the translation of the molecular events to actual locomotion shows a considerable *Divergence* in the different cell types. It is evident that the mechanisms leading to motive force generation must be controlled by regulation mechanisms, some of which have become apparent during the past years.



Obviously, contraction phenomena of cytoplasmic actomyosin, polymerization processes of tubulin or actin and membrane flow phenomena are not sufficient to explain the complicated patterns of cytoplasmic streaming involved in cell locomotion. Contraction can only result in a linear approximation of two cytoplasmic areas or, as a continuous sliding (shearing movement), in unidirectional streaming movements. Polymerization processes of actin and tubulin, on the other hand, have primarily morphogenetic functions which result in unidirectional translocation of cytoplasmic material but cannot, by themselves, explain the complicated patterns of cell locomotion.

For this reason, the processes leading to primary force generation, while operating in a certain conformance, need translation mechanisms by which the motive force is converted to locomotion. According to our experience with different objects, such as free-living amoebe, acellular slime molds and tissue culture cells, we have to consider that the transformation processes show a great divergence in different cell types. Therefore, they have to be studied separately for each cell type, and no prediction can be made from one cell type to another. Furthermore, the divergent transformation processes are modu-

lated by internal and external stimuli and, accordingly, we have a corresponding divergence in the modulation mechanisms of different cell types.

Whether the assumption of a conformance during primary motive force generation and a divergence at the level of translation to locomotion may be of heuristic value or not, we must clearly differentiate between two phenomena during cell locomotion: the generation of the linear motive force by chemomechanical energy transformation on the one hand, and the spatial transformation on these forces to complicated cytoplasmic streaming and locomotory phenomena on the other hand.

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If we now consider motility as a factor of invasion, we must first evaluate the sources of our information. There is indirect morphological evidence of various kinds. Due to their small dimensions, many *in vitro*-models of tumor penetration can be completely surveyed by histological techniques. They thus provide convincing—although static—indication of the advance of cancer cells in cultured tissues. A cautionary interpretation, however, is necessary, as pointed out in the comparison of two- and three-dimensional models. Static morphological evidence for the contribution of cell motility to invasion can also be obtained by analyzing histological preparations from the invasion zone *in vivo*. This evidence is based on the shape of the cancer cells and on the condition of their contractile proteins, in particular of actin. On the other hand, direct evidence must be dynamic and can only be provided by microcinematography. Although the applicability of this technique to the *in vivo*-situation is restricted, enough basic observations are available to justify some reflections on cancer cell locomotion within living tissues.

Comparison of Invasion in Two-Dimensional Versus Three-Dimensional Systems

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LOCOMOTION, destruction and phagocytosis are cellular functions that presumably are involved in invasion. For the past 2 yr we have investigated the influence of potentially anti-invasive agents on these cellular activities [1, 2]. During our studies we have used various *in vitro* techniques, the choice of which was frequently determined by a need for direct observation of these cellular activities.

These techniques fall into two categories: (1) Two-dimensional systems, where the cells are maintained as a monolayer on artificial substrates; (2) Three-dimensional systems, where cells or tissues form nodules or aggregates, maintained either on a non-adhesive semi-solid substrate, or in fluid medium without contact with a solid substrate.

Our results will be discussed with regard to locomotion, destruction and phagocytosis.

Locomotion

Our model for locomotion of epithelial cells is the wounded lower layer of the chick blastoderm [3]. In the whole blastoderm, as well as in the lower layer isolated on an artificial substrate (glass or plastic), the cells at the edges of a wound migrate to close the wound. However, the histology and the ultrastructure of the edge cells in the blastoderm is so different from that of the same kind of cells on the artificial substrate that we doubt if locomotion occurs in the same way in both situations. In the blastoderm, the edge cells show multifarious extensions, most of which are filopodia, attached to the basement membrane of the ectoblast. We have not been able to identify microfilaments in these lower layer cells. In contrast, on the artificial substrate, the cells of the lower layer flatten and cells at the edge of the wound show large lamellipodia, some of which end in short filopodia. In addition, lower layer cells cultured on artificial substrates are filled with microfilaments, which are organized in bundles at the level of the lamellipodia.

This example raises the general question if locomotion of a cell on an artificial substrate,