antibody interact to reduce glycolytic function. Concomitant with the glycolytic depression, there is apparently some tendency to increased respiratory activity. This suggests that the interaction of antigen and antibody tends to force a change-over, in the affected cells, from the primary glycolytic metabolic pathway, to the secondary, or oxidative, pathway. Such a change-over might reasonably be expected to decrease the viability of the affected cells, and consequently their fertilizing capacity.

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Haptotaxis and the Mechanism of Cell Motility

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Dr. Carter puts forward a hypothesis for the basis of tissue cell motility involving considerations of thermodynamics. He uses it to explain experimental haptotaxis and other features of cell motility such as ruffling and circus movement. Dr. Moilliet shows that the hypothesis is thermodynamically feasible

In a previous article[1] I described the motility of cultured tissue cells on specially prepared surfaces. The cells used in these experiments did not adhere to surfaces of pure cellulose acetate, but adhered readily if the acetate surface was previously coated with evaporated palladium.

By controlling the amount of palladium deposited, it was possible to make a range of surfaces which gave different degrees of cell adhesion. Experiments with these surfaces emphasized the importance of the underlying substrate in determining cell behaviour. For example, "*L*" cells showed mutual contact inhibition[2] on a surface to which they adhered strongly, but not on one to which their adhesion was relatively weak. Other experiments involved a gradient of progressively increasing metal deposition on a surface of cellulose acetate. Such a surface presents a corresponding gradient of cell to substrate adhesion, and cells were found to move up this adhesion gradient in a highly directional manner. I called this phenomenon "haptotaxis", and suggested that cell movement from a less adherent to a more adherent surface is the dominant principle in tissue cell motility. I indicated how all movements of tissue cells could be interpreted on this basis, and considered particularly how the principle of haptotactic movement could be applied to chemotaxis and to cancer invasion.

The present paper attempts to relate the phenomenon of haptotaxis to the mechanism of cell movement. This is necessary if it is to be established as a general and overriding principle of tissue cell motility.

As in previous experiments, the cells used were mouse fibroblasts (Earle's "*L*" strain). These were cultured in Eagle's medium[3] (with 8 per cent heat inactivated calf serum), using oil sealed culture chambers[4]. The technique of preparing cellulose acetate films on cover glasses was described in the previous paper[1].

Tissue cells depend for their motility on attachment to a suitable substrate. True motility involves the displacement of the whole cell in relation to this substrate. In the simplest analysis, the movement of a cell on a solid material such as glass involves two prime requirements: the leading margin of the cell must move forward, and the trailing margin must follow in the same direction. It is convenient to consider these requirements separately.

Movement of the leading margin. A thin film of cellulose acetate on a cover glass can be scraped to expose areas of underlying glass. When the leading margin of a cell moving on the exposed glass meets the edge of the acetate film, forward movement ceases immediately.

This behaviour resembles the "contact inhibition" which occurs when a cell meets another cell moving on glass, and the operative mechanism appears to be the same.

Fig. 1 shows a cell approaching the edge of a film of cellulose acetate, and the same cell shortly after it has made contact with the film. It will be seen that the film completely blocks the forward movement of the cell. If the acetate surface is sufficiently clean, no visible extension takes place over it. The simplest and most satisfying explanation for this effect is that the leading

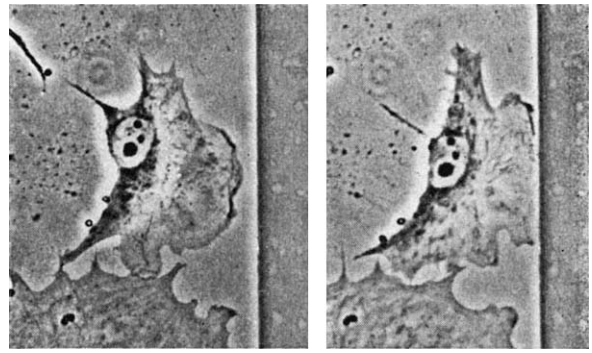

Fig. 1. A cell on glass approaching the edge of a cellulose acetate film and the same cell after making contact with this edge. Forward movement of the leading margin of the cell ceases as soon as contact is made. (Phase contrast × 375.)

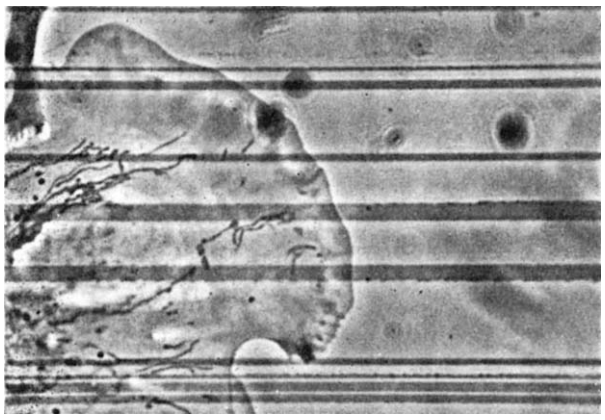

Fig. 2. The leading margin of a cell moving on a surface of alternating strips of cellulose acetate and glass. The margin bulges forward on the lighter (glass) strips, and is held back on the darker (acetate) strips. (Phase contrast × 1,000.)

edge of a cell moving on glass extends by passive spread, and not by forces arising inside the cell. The glass provides a wettable surface on which spreading can occur, but the acetate presents a surface which cannot be adequately wetted by the cell. In the same way a drop of water spreading on a glass plate will stop spreading exactly at the edge of a film of grease.

Further evidence for the passive nature of cell extension is provided by the appearance of a cell moving on a substrate consisting of alternate strips of cellulose acetate and glass (Fig. 2). The leading edge of this cell is seen to bulge forward on the lighter glass strips, and to be held back on the darker acetate strips. The same pattern is evident when a drop of gamma-globulin solution (for example) spreads passively on the same type of surface (Fig. 3).

Weiss[5] argues that the expansion of the cell surface at an interface cannot be regarded as a basically passive process. In support of this he cites the finding of Lettré[6] that cells dosed with ATP tend to remain extended instead of rounding up when undergoing mitosis. Even if it were shown that the presence of ATP at or near the cell surface is a necessary requirement for cell extension, this would not exclude the possibility that such extension depends on passive spread. All that is implied by "passive" in this context is that the final process in the movement of the leading edge of the cell involves intermolecular forces acting between the surface of the cell and the surface of the substrate. Metabolically derived energy can be represented in the form of surface free energy as well as any other, and there is no reason why it should not act in this form to bring about cell movement. In fact the terms "active" and "passive" applied to particular processes become meaningless when considered at the molecular level. Nevertheless I think the concept of passive spread (as defined) is valuable in attempting to understand the mechanism of cell movement, provided it is not taken to mean that the cell does not contribute any energy to the process.

The nature of the forces concerned with cell adhesion is poorly understood and largely disputed. Curtis[7] has used interference reflexion microscopy to investigate this problem. He has calculated that the closest approach of the cell surface to a glass substrate is about 100 Å. This type of calculation necessarily involves making a large number of assumptions, but there is also the tacit assumption that this gap is constant in width over an unspecified area of surface. The size of this area depends on the resolving power of the method as a whole, but this cannot be better than the optical resolving power of the microscope. Even at its theoretical minimum, therefore, this area will be very large in relation to a gap of 100 Å. It seems highly unlikely that a macromolecular surface would present a regular contour on this scale.

If a gap of this order does exist, then it cannot strictly be said that the glass is wetted by the cell surface. Nor can the relationship of the two surfaces be considered by reference to a single interfacial or boundary tension. Until these problems are settled, however, it seems preferable to use these terms provisionally, as there is no virtue in introducing new terminology before it can satisfactorily be defined.

The idea that surface tension forces are involved in cell motility is a very old one. In 1886 Berthold[8] interpreted amoeboid movement in terms of local variations in surface tension, and Rhumbler[9] extended these ideas further. Many other workers adopted a similar approach to problems of cell movement. Harvey[10] gives a useful historical summary of this early work.

Theories of cell movement which involve surface tension forces have now become unfashionable. When they are mentioned at all it is usually to exclude them from serious consideration. The older ideas regarded the cell as a drop of protoplasm of which the surface simply represented the outermost exposed layer of this material. The realization that the cell was surrounded by a distinct membrane completely invalidated this earlier concept, but the presence of a membrane does not in any way exempt the cell from the influence of forces due to boundary tensions. Naturally, the membrane will modify the effect of these forces on the cell as a whole, and the properties of the membrane as a physical structure must be taken into account.

Cells can, of course, extend into a liquid medium in the total absence of an extraneous surface. Such extensions are usually small and occur during anaphase "boiling" for example. Free extensions of this type are not in any way incompatible with the idea of passive spread on a surface. Both types of extension can be interpreted as a local reduction in the boundary tension at the cell surface. In the case of a free extension this could be due to local differences in the distribution of a surface active material. In the case of passive spread the wettable surface itself may lower the boundary tension at the point of contact.

Movement of the trailing edge. When considering the movement of the trailing edge of the cell, it is helpful to distinguish the situation in which a cell is moving on a gradient of adhesion from that in which it is moving on a uniform surface.

In the case of an adhesion gradient (such as that produced by a graded deposition of palladium on cellulose acetate), the margin of the cell which lies highest on the gradient will be subject to the greatest spreading tension. Correspondingly the opposite margin, on a lower part of the gradient, will be in contact with a less wettable surface and subject to a lower spreading tension. If the gradient

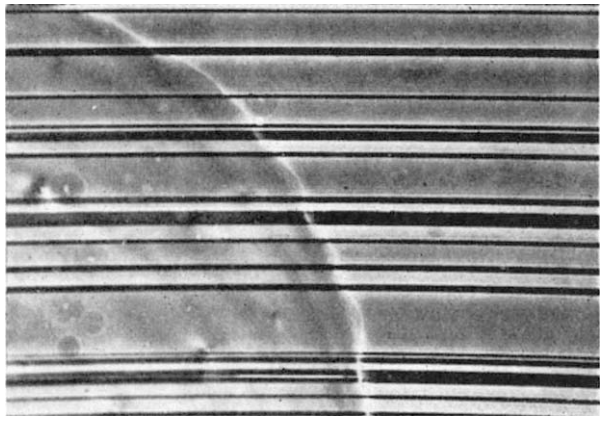

Fig. 3. The margin of a drop of gamma-globulin solution spreading on the same surface as that shown in Fig. 2. The margin of the drop presents the same pattern as the margin of the cell, bulging forward on the glass strips and held back on the strips of cellulose acetate. (Phase contrast × 480.)

is sufficiently "steep" and the cohesive forces of the cell sufficiently strong, then the stronger pull on the side of the cell farthest up the gradient might be sufficient to draw the cell bodily up the gradient. In theory at least, the cell could move up such a gradient without expending any metabolic energy, since it will have moved to a position of lower total free energy. In practice, however, with artificial gradients of this type, I think that the energy contributed by the gradient itself represents only part of the energy required to move the cell. This contribution is nevertheless sufficient to determine its direction of movement. For the rest it is necessary to invoke the kind of mechanism which I shall propose for movement on a uniform surface.

Before discussing this mechanism, it may be useful to consider certain aspects of the nature of adhesion. For present purposes adhesion will be considered in terms of relative wettability. When a cell adheres to a glass surface it is commonly described as though the only surfaces involved were those of the cell and the glass. But this is fundamentally a system of three phases in which the cell, the glass, and the fluid medium in which they are immersed all need to be considered equally. This means that the medium/glass interface is not only relevant to the adhesion of the cell: it should be accorded exactly the same importance as the cell/glass interface. Indeed, the adhesion of a cell to a solid surface represents a three way competition, each phase being competed for by the other two. In the argument which follows, however, the consequences of changes at the cell/medium interface will not be considered, and for descriptive purposes the adhesion of the cell will be discussed in an over-simplified form in terms of a competition for the solid surface between the cell and the medium. The concept of a cell failing to adhere because the adhesion forces between it and a particular surface are too weak is incomplete. Adhesion may also fail because the adhesion forces between the medium and this surface are particularly strong. This would enable the medium to displace the cell from contact with it. A drop of oil may spread on a glass surface in air, but the same oil may fail to spread on glass under water because the water can successfully compete with it for the glass surface.

To return to the subject of cell movement on a reasonably uniform surface such as glass, the problem is to account for the fact that the trailing margin of the cell moves in the same direction as its advancing margin. If the movement of the advancing margin is due to passive spread, this spread would be expected to be equal in all directions. In the case of a cell showing directional movement on such a surface, this is clearly not the case, and it is necessary to find a reason for this loss of symmetry.

Using the technique of ellipsometry, Rosenberg[11] has investigated the submicroscopic layer of material which appears to be deposited by cells when in contact with certain substrates such as chromium coated glass. He called this material a "microexudate" and considered that it was transferred directly to the substrate by contact with the cell, since none could be demonstrated in the supernatant from cell suspensions. Chemically it appeared to be a complex of materials including protein. Rosenberg also showed that culture media containing serum very rapidly produced an adsorbed layer of protein on chromed glass. Microexudate also appeared to be deposited on such a protein film when cells were cultured on it, though the rate of deposition was reduced. The probable existence of an adsorbed layer of protein should clearly be borne in mind when considering surfaces in contact with media containing serum, and all the experiments described here were carried out in the presence of serum.

Taylor[12] has investigated the adhesion of cells to a variety of different substrates. He found that the adhesion of cells to glass is greatly reduced if the glass is covered by a layer of microexudate produced by previous contact with cells. The loss of cell adhesion on glass surfaces "contaminated" by microexudate could be due to a reduction in the affinity of the altered glass for cell surfaces corresponding to an increase in the cell/glass boundary tension. As we have seen, however, an equally possible explanation is that the affinity of the glass for medium has been increased, corresponding to a reduction in the medium/glass boundary tension. In fact this is the more likely explanation, since if the substance responsible for this effect is transferred by direct contact, it is highly improbable that such a transfer could result in an actual increase in the boundary tension between the contacting surfaces.

If a cell margin which is spreading passively outwards on a wettable surface such as glass should be momentarily reversed at a particular point, then a small area of glass which has been contaminated by microexudate (by contact with the cell) would be exposed. If the wettability of the contaminated glass for medium is increased as suggested, this could enable the medium to compete successfully with the cell and displace it from the glass at this point. The reversal of the cell margin which is necessary to initiate this process has only to expose a very small area of altered glass surface. A random Brownian event may well be sufficient for this purpose.

The situation is now no longer symmetrical, and a potential direction of movement has been determined. The medium would be expected to continue to displace the cell from the glass where the contaminated area is exposed, so that this becomes the trailing margin of the cell. The leading margin is now able to advance on uncontaminated glass with improved efficiency. This is because it is relieved of the opposing tension of the opposite cell margin transmitted by the cohesion of the cell. These factors would tend to reinforce each other, so that once the direction of the cell has been randomly determined this direction would tend to be preserved, provided the newly encountered surface is homogeneous and free of the contaminating influence of other cells.

In practice, when a cell is newly seeded on glass, it may be a considerable time before one margin of the cell gains a sufficiently strong advantage over the others to result in directional movement. Many "random" reversals of outward spread may occur before a sufficiently asymmetrical position is established to ensure continuity of movement in a particular direction. Until this position is reached, the cell may undergo many changes of shape and minor shifts of position. In marked contrast to this, directional movement on an adhesion gradient is immediate.

The suggestion that the trailing margin of a cell moves forward because it is displaced by medium may seem an even more "passive" movement than that proposed for the leading edge. Again there is no intention of suggesting that the cell does not provide energy for its own movement. Although no attempt is made here to identify the energy conversions involved, it should be borne in mind that the driving force of the medium would be provided on this theory by the surface active material deposited by the cell. This material would require the expenditure of metabolic energy for its synthesis, and in the process of movement it would need to be continuously replaced.

A basically similar mechanism may be operating to produce the curious phenomenon of circus movement which Holtfreter and others have described for certain embryonic cells[13]. In contact with glass these cells may produce a bleb of cytoplasm which protrudes at one side and proceeds to move round the periphery of the cell. When speeded up by time lapse photography each cell appears to be spinning in a clockwise or anti-clockwise direction. Again the direction of movement of the cytoplasmic bleb may be the consequence of a random event which tips the balance in a particular direction. For reasons already discussed the bleb would be expected to continue round the cell, its leading margin being drawn on by passive spread, and its trailing margin giving way

to the medium as a result of a surface active material deposited in its wake. It is only necessary to postulate that this material is desorbed or otherwise inactivated after an interval of time, so that it is reduced or rendered less effective by the time the bleb has gone full circle. The bleb would then continue to move round the cell indefinitely.

If adhesion is considered in terms of the relative success of the cell in its competition with the medium for contact with the glass, then the mechanism of movement proposed for tissue cells on a homogeneous surface such as glass may also be considered as representing a movement from a surface offering relatively poor adhesion to a surface offering better adhesion. Seen in this way, the movement of the cell on a uniform surface is also an example of haptotactic movement. Indeed, the only distinction between this and movement on a surface representing an adhesion gradient is that the cell is considered to be creating its own adhesion differential as it moves. An important consequence of this is that once the cell is in motion and has established its own adhesion gradient, it may continue across a line dividing two dissimilar surfaces in the "wrong" direction, that is towards the surface offering the lower relative adhesion. This is because the differential generated by the moving cell may represent a greater difference of adhesiveness than that between the two dissimilar surfaces.

The ruffled membrane. The picture of cell movement so far presented has taken no account of the ruffled membrane. Ruffling movements of the cell membrane are characteristic of many tissue cells moving on glass, and are well shown by the "*L*" cell. Ruffling can occur at any margin of the cell in relation to its direction of movement, and it is by no means confined to the leading edge. Nevertheless, there is a tendency in rapidly moving cells for the ruffled membrane to be more fully developed at the front of the cell, and the trailing margin may show no ruffling at all. For this reason it has been suggested[14] that the ruffled membrane may be looked on as the "organ of locomotion" of cells which demonstrate this type of behaviour. This view is widely held, and theories of cell movement[15] have been based on the idea that the ruffles are essentially wave-like in character, and that their rearward movement across the surface of the cell is responsible for the forward movement of the cell as a whole. The formation of a ruffled membrane, however, is dependent on a surface (such as glass) which offers a relatively high degree of adhesion. "*L*" cells, for example, remain essentially spherical on a surface offering little adhesion (such as cellulose acetate), and do not show any ruffling, yet they are able to move as efficiently as on glass. It is probably misleading, therefore, to regard the ruffled membrane as the organ of locomotion of the cell.

In order to interpret the ruffled membrane, it is first of all necessary to have an accurate picture of the physical pattern which it presents. Even with the help of time lapse cinematography, this pattern is complex and difficult to follow. Cells which have been trypsinized and newly seeded on glass are particularly valuable for investigating the pattern of ruffle formation. In many cases these cells attach and spread out without ruffling. The first ruffles to appear tend to be single and isolated, so that their formation can be observed critically, and a clear sequence of events can be followed. Fig. 4 shows such a cell photographed at intervals against a reference grid. The first photograph shows the cell spreading outwards, presenting the regular circular outline which would be expected for passive spread on a uniform surface. In the second photograph the cell margin has extended further. The cell outline is less regular but there is no true ruffling. The first ruffle appears in the third photograph, and is indicated by a long arrow. Reference to the grid lines shows that the formation of the ruffle is accompanied by a retreat of the cell margin at this point. The ruffle itself appears to be formed by the piling up of cytoplasm as the

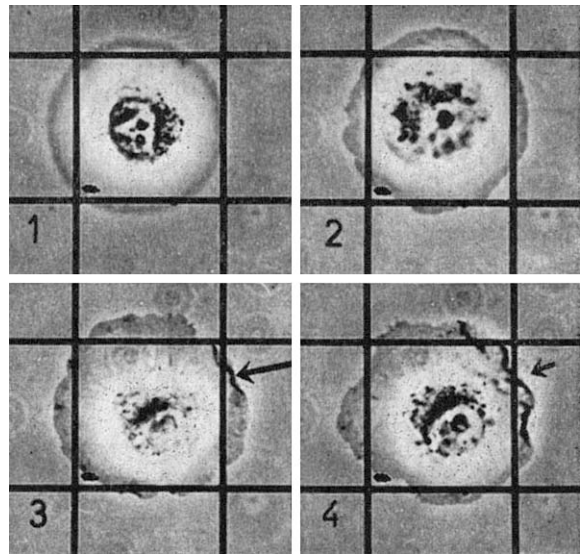

Fig. 4. A trypsinized cell, newly seeded on glass and photographed at intervals against a reference grid to illustrate the development of the ruffled membrane. The arrows indicate features mentioned in the text. (Phase contrast × 800.)

cell margin moves back. Apart from this initial movement, there is no tendency for the ruffle to be propagated backwards over the surface of the cell. The fourth photograph shows a rounded extension (indicated by a short arrow), reappearing in the same region. This extension will in turn retreat to form another ruffle. This sequence can also be seen in the fully developed ruffled membrane, but its essential simplicity is obscured by the number of ruffling movements which are then superimposed.

This pattern of movement can be interpreted in precisely the same way as I have attempted to interpret the movement of the cell as a whole. Each ruffle represents a retreat of the cell margin in the face of medium which is successfully competing with the cell at that point by virtue of the microexudate deposited by the cell. The re-extension of this margin can occur when this material has become partly desorbed or inactivated, as discussed in relation to circus movement.

Little is known about the way in which additional cell membrane is made available to accommodate new cell extensions. Whatever the mechanism, there must be a limit to the rate at which new membrane can be made available, and this may be an important controlling factor in the rate of cell extension. Ruffling is seen particularly when the cell is well spread, and the cytoplasm may form an extremely thin layer at the front of the cell, except where it is locally thickened as a ruffle. In this situation the local resources for providing new surface membrane to allow further extension may be particularly limited. If these resources become momentarily exhausted, the advancing margin must stop, and at this point the margin may be especially vulnerable to the random thermal factors already discussed which could initiate the reversal of the cell margin. The reversal itself would be checked by the development of tension in this part of the membrane as a result of the movement of other parts of the margin which are still making forward progress.

If this is a basically correct interpretation of ruffle formation, then, far from representing the organ of locomotion of the cell, the ruffling of the membrane actually impedes the progress of the cell. This is because each ruffle may be regarded as a temporary set-back to the forward movement of the leading cell margin.

In so far as ruffling may reflect the principles which determine cell movement, however, the detailed study of ruffle formation is highly relevant to the investiga-

tion of cell motility. In this context, the behaviour of recently trypsinized cells may be of particular value. Superficially, the failure of such cells to show ruffling movements until they have fully recovered from their exposure to trypsin suggests that this enzyme may destroy some component of microexudate on which ruffling may depend, or that it interferes in some way with microexudate production. Rosenberg[11] has presented evidence that trypsin adsorbed to the cell surface may continue to be active in this way.

It is still necessary to explain the relative or total lack of ruffling at the trailing margin of the cell.

Since the interpretation of ruffle formation previously discussed involves the alternate spreading and retreating of a thin layer of cytoplasm, it depends for its continuation on the continued ability of the cell margin to extend. The surface relationships of the cell membrane at the trailing margin do not favour extension, and the general state of tension in the membrane in this region (as evidenced for example by the tautness of the cytoplasmic strands which are often dragged behind the cell during its progress also militates against the local expansion of the membrane which extension must involve. It is noticeable that should this tension be generally or locally relieved by a change in cell direction, for example, ruffling at the trailing margin is resumed. When a cell on glass meets the edge of an acetate film, or demonstrates "contact inhibition" on meeting another cell, there is also a tendency for ruffling to be reduced or cease at the contacting margins. This could again be because the initial extension on which the formation of a ruffle depends is now restricted.

Although the mechanism of cell movement here proposed is basically very simple, a more complete interpretation along these lines becomes extremely complex. This is particularly true if the potential influence of the boundary tension between the inner surface of the cell membrane and the cytoplasm is taken into account[16]. Each situation demands the consideration of a number of factors which may sometimes oppose, and sometimes support, each other. In addition it will seldom be clear in a given instance which are the main factors concerned and which make only minor contributions. A local feature of a moving cell may have an essentially local explanation, but it is also liable to be influenced by situations obtaining elsewhere in the cell. In assessing the relative importance of these factors, it would be extremely useful to know, for example, to what extent the forces due to a spreading tension at one margin of the cell may be transmitted to another part of the cell by tension in the cell membrane. This problem would be complex enough if the cell membrane were a stable structure, but the fact that it may be in a dynamic state, involving the continuous interchange of material between the membrane and the cell interior, could make its formal solution virtually impossible.

The theory of cell movement I have put forward does not invoke any internal mechanisms for moving the cell, such as specialized contractile elements. If such mechanisms can be shown to exist in a particular type of cell, they must clearly be taken into account. Apart from this, the theory is intended as a general basis for the motility of all types of tissue cell. On the other hand it is not intended to apply in this form to the mechanism of "true" amoeboid movement such as that shown by *Amoeba proteus*.

The purpose of investigating the movement of tissue cells *in vitro* is to try to identify the principles which govern their motility, in the hope that these principles may also be applied to such cells in their normal environment *in vivo*. Extrapolation of *in vitro* results in this way is a hazardous but necessary step. In attempting to transfer these ideas to their proper context in the living animal, an important question is raised: to what extent may the movement of a particular cell be due to "pre-existing" gradients of surface adhesion presented to it, and to what extent could it be due to a gradient of the cell's own making? If it is mainly a question of pre-existing adhesion differentials which are presented to the cell, then a rather disturbing possibility has to be entertained—that cell movement on artificial materials such as glass may be dependent on a mechanism which is largely irrelevant to cell movement *in vivo*.

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Elementary Surface Thermodynamics of Carter's Theory of Haptotactic Cell Movement

THE mechanism of haptotactic cell movement proposed by Carter[1,2] can readily be shown to be feasible in terms of the thermodynamics of surfaces, provided that the inner and outer surfaces of the cell membrane can be treated as interfaces with positive boundary tensions. The simplest case is represented in Fig. 1, which shows the cross-section of a cell, represented as a droplet of liquid (2), on the surface of a solid substrate (3), in competition with another liquid (1). Suppose now that γ^y_{13}, the value of the interfacial tension (1)–(3) at Y, is less than the value γ^x_{13} at X. As Carter has pointed out, this could be due to a surface free energy gradient on the surface of the solid, produced for example by differential metal shadowing. Alternatively, or perhaps at the same time, a surface-active material might be adsorbed or deposited at the (2)–(3) interface and the droplet slightly displaced by accident to the left, leaving a "contaminated" (1)–(3) interface of lower interfacial tension immediately to the right of Y.

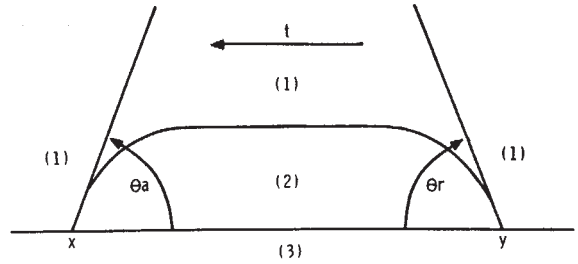

Fig. 1.

The net spreading tensions at X and Y are given respectively by

$$t_a = \gamma^x_{13} - \gamma^x_{23} - \gamma^x_{12}\cos\theta_a \quad \text{(to the left)}$$

and $$t_r\gamma = \gamma^y_{13} - \gamma^y_{23} - \gamma^y_{12}\cos\theta_r \quad \text{(to the right)}$$

the resultant tension (to the left) being

$$t = t_a - t_r = (\gamma^x_{13} - \gamma^y_{13}) - (\gamma^x_{23} - \gamma^y_{23}) - (\gamma^x_{12}\cos\theta_a - \gamma^y_{12}\cos\theta_r)$$
$$= \Delta\gamma_{13} - \Delta\gamma_{23} - (\gamma^x_{12}\cos\theta_a - \gamma^y_{12}\cos\theta_r) \qquad (1)$$

θ_a and θ_r not necessarily being equilibrium contact angles.

It is clearly a possible condition that the values of the γ's be such that t is greater than zero. On a differentially