[11] Koshland, D. E., Jr., Y. D. Karkhanis, and H. G. Latham, *J. Am. Chem. Soc.*, **86**, 1448 (1964).
[12] Hartley, B. S., in *Enzyme Models and Enzyme Structures*, Brookhaven Symposia in Biology, No. 15 (1962), p. 85.
[13] Koshland, D. E., Jr., D. H. Strumeyer, and W. J. Ray, Jr., in *Enzyme Models and Enzyme Structures*, Brookhaven Symposia in Biology, No. 15 (1962), p. 101.
[14] Newbery, G., and M. A. Phillips, *J. Chem. Soc.*, 3049 (1928).
[15] Schwert, G. W., and Y. Takenaka, *Biochim. Biophys. Acta*, **16**, 570 (1955).

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*THE DYNAMICS OF THE MEMBRANE-BOUND INCOMPRESSIBLE BODY: A MECHANISM OF CELLULAR AND SUBCELLULAR MOTILITY**

BY PAUL WEISS

THE ROCKEFELLER INSTITUTE

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Let us start from the widely accepted Danielli-Davson model of the cell surface as a composite sheet consisting of transversally oriented lipid molecules on the outside, lined by a tangentially oriented network of protein chains underneath. If we view this smectic system not in its customary schematized representation as an open fragment with a free edge, but in its natural configuration of a closed system, it reveals dynamic properties of great biological significance not formerly recognized. The real structure differs from its schematic sample in two regards: (1) it is a *continuous* two-dimensional body, completely closed up within itself; and (2) it envelops a closed space filled with substance of high water content, hence, very low compressibility (to be referred to in the following as "core").

The properties emerging from this configuration rest on the following premises: (*a*) The average population density of the molecules in the lipid "picket fence" is determined by the equilibrium between the cohesion due to van der Waals' forces and the dispersive pressure exerted from the enclosed core. (*b*) The surface membrane constitutes a permeability barrier between the outside medium and the core. (*c*) The permeability of the surface layers increases with increasing intermolecular distances: widening of intermolecular "pores" renders the membrane "leaky." Assuming water in the core to be mostly in bound and polymerized form, the increased flux pertains chiefly to ions and small molecules. (*d*) The lipid layer is "spot-welded" to the polar side chains of the underlying protein layer by electrostatic bonds, so that any local deformation of either layer is mechanically transmitted to the other. (*e*) There is potential energy ("strain") stored within the system which upon local release can effect contraction of the protein net; by changing the array and packing density of the molecules of the surface membrane, this contraction engenders local deformations. (*f*) Increased flux of ions and molecules across the membrane according to (*c*) can activate the energy release cited in (*e*).

Let us now consider a cylindrical core of fluid or semifluid substance of negligible compressibility, completely enveloped by a membrane of the listed properties. Let then one end (hereafter called "proximal") of this cylinder become the site of a chemical, electrical, or mechanical alteration that causes the molecules of the sur-

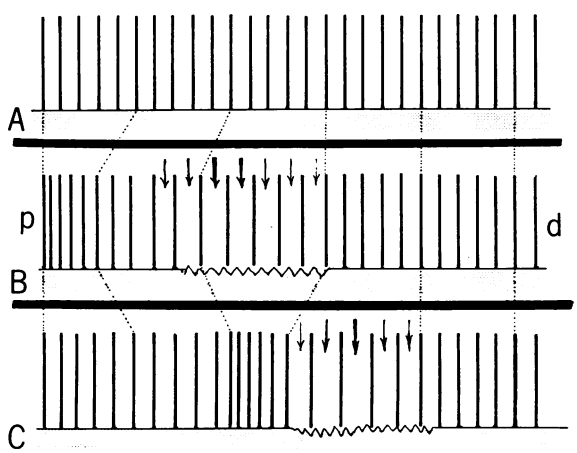

FIG. 1.—Diagram of wave of molecular packing density and concomitant permeability change in lipid-protein surface film. (*A*) "Resting" equilibrium. (*B*) Disturbance at proximal (*p*) end; arrows indicating flux through intermolecular "pores"; zigzag, protein contraction. (*C*) Advance of wave in distal (*d*) direction.

face membrane to become more tightly packed in that region than they have been in their former equilibrium state (Fig. 1*B*). Such a local condensation of the surface will necessarily entail the following train of reactions (Figs. 1 and 2).

(1) A reduction of intermolecular distances in a given surface area by an average of $n\%$ (Fig. 2*B*, 1→2) amounts to a shortening of the circumference of the cylinder by n per cent. The corresponding reduction of the cross-sectional area of the enclosed space then equals $n/100\ (200 - n)$ per cent; for instance, scalar surface shrinkages of 10 or 20 per cent subject the corresponding core portion to constrictions of 19 or 36 per cent, respectively (Fig. 2*A*).

(2) Any such local constriction of the incompressible, yet deformable, core content obviously forces substance from the shrinking into the unrestrained portions. In the case of our cylinder, in which the constriction started at the blind proximal end, the only escape for the expressed content is into the distally adjoining portion; the latter thereby becomes enlarged. For substances of high viscosity, this enlargement takes the form of a bulge tapering distally (Fig. 2*A*).

(3) This bulbous enlargement stretches the surface envelope; hence, it increases the intermolecular distances between the lipid surface molecules (Fig. 1, *A*→*B*).

(4) In consequence, according to (*c*), local permeability in the region of the bulge goes up.

(5) The resulting flux of ions and molecules across the leaky membrane region then initiates reaction (*f*); that is, it releases energy in the part of the system underlying the "leak," which in turn engenders contraction of the stretched tangential protein network around the bulge (Fig. 1, *B*→*C*). After its passive expansion, the bulge thus passes automatically into a phase of active contraction.

(6) This secondary compression of the bulge then forces the previously entered excess of material out again.

(7) At the same time, the puckering of the contracting protein layer (Fig. 2*B*) brings, according to (*d*), the molecules of the attached lipid layer back into closer

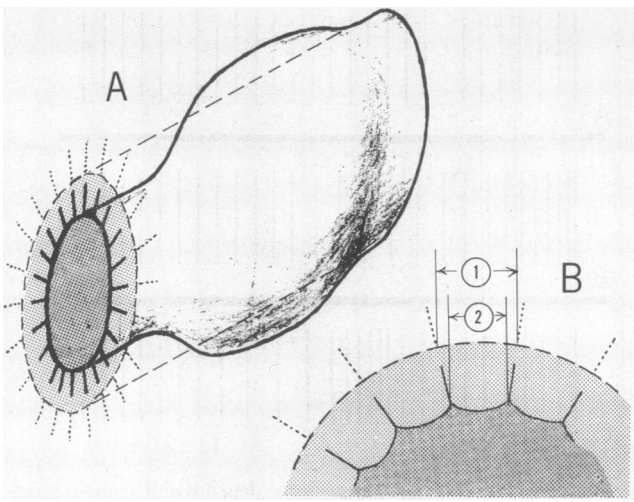

FIG. 2.—Deformation (solid lines) of incompressible cylindrical core (broken lines) by terminally initiated contraction. (*A*) Formation of traveling "bulge." (*B*) Cross-sectional shrinkage due to molecular tightening (change of intermolecular distances from 1 to 2) in surface.

mutual apposition, thus tightening again the permeability barrier and shutting off the transmembrane flux which had initiated the contraction.

(8) Even if, on the simplest assumption, the excess material that is squeezed from the contracting bulge escapes in the proximal (*p*) and distal (*d*) directions in equal amounts, the effect on the configuration of the column is quite asymmetrical. On the proximal side, where the column had been constricted, the return of half the excess substance from the bulge merely produces re-expansion toward the original size, while on the distal side, the same addition amounts to a positive enlargement as in (2). In short, the bulge travels distad.

(9) As can readily be seen, the whole chain of events from (3) to (8) then repeats itself in this slightly more distal location, and after that in the next farther distal one, and so on down the length of the cylinder. The result is a coordinated *micro-peristaltic wave*, propagated in the proximo-distal direction.

In summary, the dynamics of this system yield the following effects. There is a polarized shift of core substance in the distal direction. The net amount transferred in a single wave would, according to (8), be of the order of half the volume of the traveling bulge, which in the blind tube of our model, would show up as a temporary bulbous distention of the distal end. However, repetitive waves will have a cumulative effect, and the proximo-distal transfer and distal accumulation can assume major proportions; the actual magnitude will depend upon several variables, particularly the frequency of the waves in relation to the relaxation characteristics of the system.

The applicability of the model to the dynamics of the nerve fiber, the so-called "axonal flow," [1] is immediately evident. Our discovery[2] that the neuron is a moving steady-state system whose substance is continuously reproduced in the central cell body and then conveyed in a continuous feeder column cellulifugally down the nerve fiber, partly to be consumed in the replenishment of catabolically

disintegrating macromolecular systems, partly to be discharged at the distal end as transmitter agents and other "neurohumors," has made it necessary to postulate a microperistaltic wave as the driving mechanism for the convection. After some early cursory allusions to such waves in outgrowing branches of embryonic and larval nerve fibers,[3, 4] the occurrence of regular pulse waves in the surfaces of *mature* nerve fibers has recently been demonstrated cinemicrographically.[5] For this phenomenon the present model offers a compelling mechanism.

With appropriate scaling allowances, the model applies equally well to all membrane-enclosed spaces with narrow lumens filled with incompressible substance. It therefore could be viewed as a general mechanism of intraprotoplasmic transport. It could, for instance, explain the "pumping" of fluid through submicroscopic channels, such as microtubules and endoplasmic reticulum; the churning of the content of mitochondria; and the wormlike motions observed in "myelin figures."[6] Furthermore, for cores of low viscosity, one could assume that the pressure head which builds up at the distal end as a result of the proximo-distal surface wave generates the axial back flow observed in many forms of protoplasmic streaming —for instance, in plasmodial slime molds.[7]

Extrapolating now from the essentially linear or planar (tubular or laminar) configurations, considered in the foregoing, to more nearly equidimensional (e.g., spherical) cores, the model assumes the following features (the numerals corresponding to the propositions listed above numerically for cylindrical shapes). Let us initiate a local condensation at some part of the surface membrane (1). Incompressible content is thereby forced against the unperturbed rest of the membrane (2), stretching the latter accordingly, and hence increasing its permeability (4); as a result, the stretched part now changes from passive dilation to active contraction (5), thus pressing, in its turn, content against other sectors that are still slack or have already relaxed from their earlier contraction. The whole sequence of steps then repeats itself in the shifted location. In this manner, contraction-relaxation waves, once initiated, sweep over the surface of the body incessantly, manifesting themselves as rhythmic pulsations of the total mass.

While most conspicuous in the yolk of certain fish eggs and cultured glia cells,[8] similar pulsations have also been seen in many other cells in tissue culture[9] and are conceivably a general feature of living cells with freely exposed surfaces. Depending on the consistency and the structural restrictions of the cell content, as well as on the degree of uniformity of the cell membrane, they range from smooth heaving motions to traveling bursts of surface protrusions.

In the general case just discussed, the circling character of the sweep accounts for the property of self-perpetuating rhythmicity inherent in the model, as long as the cell surface has access to a steady supply of metabolic energy for the restoration of its contracted portions to their equilibrium condition of contractility. The model thus becomes an instructive example of how sequences of coupled chemical and physical events can automatically become *mechanisms* through which ubiquitous scalar energy is channeled into coordinated vectorial effects.

In our example, the mechanism transduces chemical into mechanical energy. Since even in its simplest version, the model consists of a chain of heterogeneous processes, the kinetics of each step being limiting for the next, the relatively slow time constant for a single pulse (of the order of minutes for the quoted examples)

might pass as not altogether unreasonable. Its quantitative substantiation presents, of course, a major test for the validity of the model.

One virtue of the model is that it explains the coordinated sequential activation of large molecular populations without recourse to specific structural devices. One need only bear in mind that the surface of a "heaving" fish egg consists of roughly 10^{14} molecular domains to realize the necessity of some sort of coordinating principle to keep a major portion of that surface acting in unison.

The directionality of the propagated wave, as indicated in point (8), is due primarily to the asymmetry between the relaxed and contracted states of the surface at the leading and the trailing edge of a wave, respectively. For cores of low viscosity, one may have to consider also inertial flow characteristics, in which case repetitive surface waves could have a progressively accelerating effect on the internal convection, thereby intensifying the original polarity.

Contrary to relatively equidimensional shapes, however, the model offers no cogent explanation for self-regenerative rhythms in essentially linear systems, such as the cylindrical core from which we started. Or rather, there are several alternative hypotheses conceivable, all inconclusive. For instance, if the gradual reexpansion of surface in the wake of the wave mentioned in (8) overshoots the equilibrium condition, this would create renewed surface loosening at a given distance behind the first wave and thereby initiate another contraction wave, and so forth. One could think, as a model for our model, of the rhythmical longitudinal oscillations of a vertical coil spring, first extended and then released. In general, the problem bears resemblance to the rhythmicity of macroperistaltic waves in tissues, whether neurogenic or myogenic (e.g., those of the intestine, oviduct, ureter), but there is little ground at present for further speculation.

One additional feature of the model is its potential bearing on the problem of cell locomotion. If one assumes that the described local changes in the surface membrane also affect the local adhesiveness of its outer layer to a given substratum, one recognizes immediately how the corresponding traveling wave of surface attachment, paralleled by the peristaltic forward-pumping of the core content must result in a continuous gliding motion of the whole system over its substratum. In appearance this mode of locomotion resembles the crawling of a caterpillar, in which the peristaltic waves of the body wall are similarly synchronized with corresponding phases of limb movements. The fact that signs of longitudinal waves in advancing cells in tissue culture have actually been observed[10] speaks strongly in favor of the concept here proposed.

In concentrating on the essential features of the model, several aspects have been disregarded which are presumably relevant to its application in practice. Two of these may be briefly mentioned. Systems bounded by rather rigid envelopes or otherwise tightly confined, would not admit of actual deformations of the order illustrated in Figure 2, yet would still exhibit the properties of the model, since even without the formation of a bulge, the condensation of molecules in one region would cause, accordion-fashion, a commensurate dispersal in the adjacent region, increasing the latter's permeability, and in further consequence, contractile pressure (Fig. 1, $A \rightarrow B$). In this case, isometric pressure waves would take the place of pressure-induced isotonic deformation waves.

A second feature to be taken into account is the following. In a cohesive protein

net, the tension produced by any local contraction forces the more peripheral meshes into orientations converging upon the active region.[11] Any subsequent contraction of these preoriented fibers, therefore, has a resultant bias in the given direction, which then is passed on to the next peripheral region, and so forth. In the example of our cylinder, a bulge would thus stretch and thereby orient the protein fibers ahead of it in a predominantly longitudinal direction, thus predisposing that region for shortening lengthwise, which would facilitate its widening into another bulge. In short, a transient structure arises analogous to the longitudinal muscles of peristaltic organs—or earthworms—to act antagonistically to the radial compression of the bulge.

It is beyond the purpose of this article to go into further details. The main purpose has been to introduce the model as an example of the kind of mechanistic terms through which general scalar properties of living systems, such as are dealt with in biochemistry, can be translated into the orderly physical performances which the student of organized biological systems faces and must explain.

Summary.—Membranes in biological systems enclose spaces filled with essentially incompressible, but deformable and movable, substance. This fact has been made the basis for a model of the dynamics of such composite systems. The model can in principle account for the pulsatory transfer of substance in membrane-bound biological systems of microscopic and submicroscopic dimensions (e.g., peristalsis of "axonal flow"; churning of content of mitochondria; heaving of eggs and cells), as well as for cell locomotion. It illustrates one possible mode of converting scalar molecular activity into coordinated vectorial group effects.

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† New address: Graduate School of Biomedical Sciences, University of Texas, Texas Medical Center, Houston, Texas 77025.

[1] Weiss, Paul, in *Regional Neurochemistry*, ed. S. S. Kety and J. Elkes (Oxford: Pergamon Press, 1961), p. 220; Weiss, Paul, in *Symposium on the Effect of Use and Disuse of Neuromuscular Functions*, ed. E. Guttman (Prague: Publishing House of the Czechoslovak Academy of Sciences, 1963), p. 171.

[2] Weiss, Paul, and H. B. Hiscoe, *J. Exptl. Zool.*, **107**, 315 (1948).

[3] Lewis, W. H., *Anat. Record*, **91** (Suppl.), 25 (1945).

[4] Speidel, C. C., *Am. J. Anat.*, **52**, 1 (1933).

[5] Weiss, Paul, A. C. Taylor, and P. A. Pillai, *Science*, **136**, 330 (1962).

[6] Holtfreter, J., *J. Morphol.*, **79**, 27 (1946).

[7] Allen, R. D., and N. Kamiya, eds., *Primitive Motile Systems in Cell Biology* (Academic Press, 1964).

[8] Pomerat, C. M., *Intern. Rev. Cytol.*, **2**, 307 (1961).

[9] Weiss, Paul, in *Proceedings*, Robert A. Welch Foundation Conferences on Chemical Research, vol. 5, 1964.

[10] Ambrose, E. J., *Exptl. Cell Res.*, Suppl. 8, 54 (1961).

[11] Weiss, Paul, *Rev. Mod. Phys.*, **31**, 11 (1959).