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A Solid-Liquid Composite Model of the Red Cell Membrane

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Summary. Direct mechanical experiments and analyses support the view that the red cell membrane is a composite with a solid structural matrix, which can behave as either a viscoelastic or viscoplastic material.

In the last decade, numerous techniques have been developed to probe the membrane. Each technique tends to be specific to a different component of the membrane and leads to a specific view of membrane architecture. For example, the rapid translational diffusion of large protein "markers" in the plane of the membrane (Frye & Edidin, 1970; Edidin & Fambrough, 1973; Liebman & Entine, 1974; Poo & Cone, 1974; Edidin, Zagynsky & Lardner, 1976) indicates that membrane lipid is a two-dimensional "fluid mosaic" (Singer & Nicolson, 1972). Particular studies with human red cell membrane also indicate that the lipid is fluid (Rudy & Gitler, 1972; Aloni, Shinitzky & Livne, 1974; Solomon, 1974). However, we have developed *mechanical* techniques for studying the human red cell membrane and are led to a very different view of membrane structure (Hochmuth & Mohandas, 1972; Evans, 1973*a* and *b*; Hochmuth, Mohandas & Blackshear, 1973; Evans & Hochmuth, 1976*a* and *b*). We observe that the membrane behaves as a solid material in its response to mechanical forces. Below a yield condition, the membrane is a highly deformable viscoelastic material; i.e., a material capable of large recoverable, elastic deformations with internal viscous energy dissipation. Above the yield condition, it begins to flow in a viscous, plastic manner that results in irreversible deformation. *Four* separate material constants characterize this behavior; a shear modulus of elasticity, a shear viscosity (in the viscoelastic domain), a yield "shear", and a plastic shear viscosity. These observations support the view that the membrane is a composite material, and that our mechanical techniques *study the part of the membrane which behaves like an elastic or plastic solid*

just as other techniques probe the fluid (lipid) component of the membrane. We hypothesize that the membrane's solid-like character and the four material constants reflect the behavior of peripheral membrane proteins which form a structural matrix on the cytoplasmic surface as depicted in Fig. 1. Thus, a study of the intrinsic material constants is a direct study of the structural proteins *in situ*.

The concept that there exists a structural membrane component is not new. In their paper on the isolation of "spectrin", Marchesi, Steers, Marchesi & Tillack (1970) state that "... it is evident that spectrin is indeed an important structural component, since the intact ghosts become fragmented during the removal of spectrin, and lose a coating of filamentous material normally present on the inner surface of the membrane ...". However, once it has been postulated that a structural membrane component exists and is responsible for the membrane's solid-like behavior, it is necessary to measure the material properties of the structural component, preferably *in situ* and preferably by direct mechanical methods. This we have done.

Assumptions and Approach

We treat the red cell membrane as a *two-dimensional* nearly incompressible material which is isotropic in the plane of the membrane (Evans, 1973*a* and *b*; Skalak, Tozeren, Zarda & Chien, 1973). Two-dimensional incompressibility implies that when the membrane is deformed under the action of an applied force, it does so at *essentially constant* surface area (Hochmuth & Mohandas, 1972). (As Evans, Waugh & Melnik have shown recently (1976), only small area increases on the order of 1% occur when large isotropic tensions are imposed on the membrane.) We assume that the red cell interior is in an amorphous fluid state (Cokelet & Meiselman, 1968). Therefore, the equilibrium mechanical properties of the red cell are derived completely from the membrane.

Our approach is to separate the influence of cell geometry (an extrinsic factor) from measurements of the intrinsic material properties of the cell membrane. The intrinsic material behavior is the deformation and rate of deformation response of "infinitesimal" membrane elements to forces applied to the element, expressed by a constitutive relation between the resultants (forces distributed per unit width on the element sides) and the deformation and rate of deformation. Because large deformations occur we observe deformation and rate of deformation by measuring

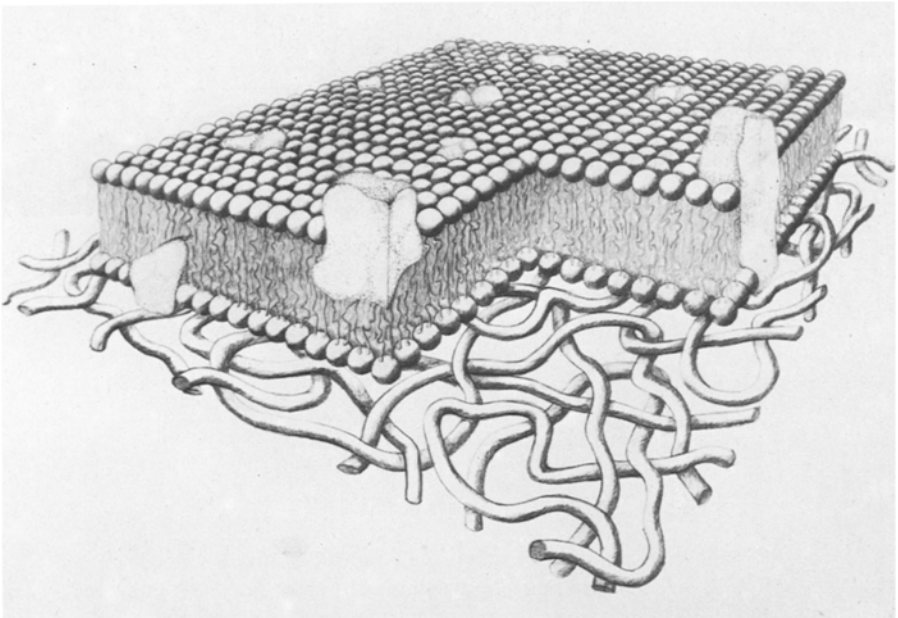

Fig. 1. Symbolic representation of red cell membrane as a solid-liquid composite. The structural "backbone" from which the membrane obtains its solid material properties is shown as a random matrix on the underside (cytoplasmic side) of the lipid bilayer-"integral" protein matrix. The lipid bilayer-integral protein (e.g., fluid) matrix component of the composite has been illustrated previously by Singer and Nicholson (1972, Fig. 3). Also, it should be noted that Bretscher (1973) has suggested *external* carbohydrate residues of glycoproteins could form a "lattice" over the cell surface

changes in an element's dimensions (extension ratios), with the element oriented in a principal axes system where only extension and constriction of these dimensions occur. Each aspect of observed red cell membrane behavior will be represented: hyperelastic solid (highly deformable with total recovery); viscoelastic solid (highly deformable with total recovery *and* with internal, viscous energy dissipation); viscoplastic solid (the maximum elastic limit has been exceeded and the material flows *irrecoverably* with viscous energy dissipation). In addition, the experiments which have been used to study this behavior will be described.

Membrane Hyperelasticity

The red cell membrane is able to undergo large elastic deformations at constant surface area (Hochmuth & Mohandas, 1972). The slow elonga-

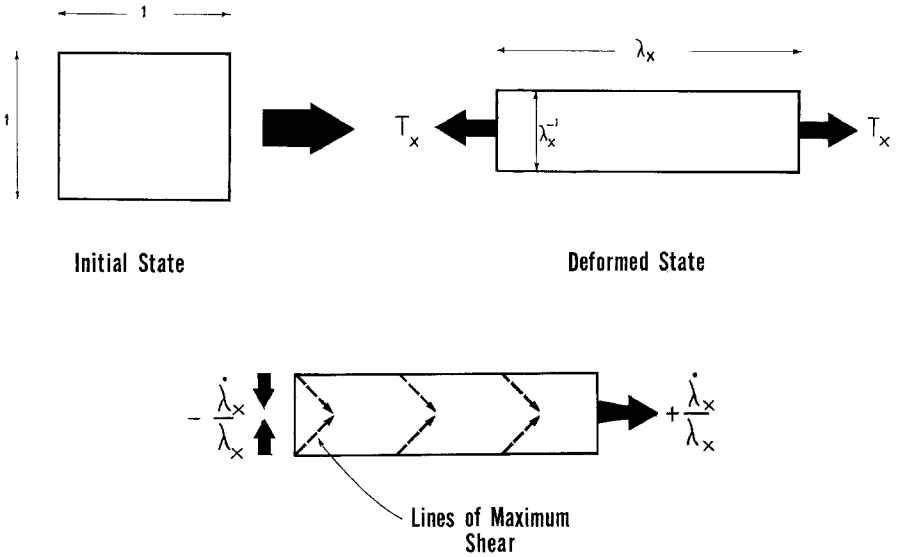

Fig. 2. The deformation of a two-dimensional, incompressible square material element into a rectangular strip. T_x is the uniaxial membrane tension, λ_x is the extension ratio, and $\dot{\lambda}_x$ is the rate of extension, in the x direction. The extension ratio in the y direction, λ_y, is equal to λ_x^{-1}

tion of a two-dimensional, incompressible membrane material element (Fig. 2) by the action of an in-plane uniaxial tension, T_x, can be represented by a first-order tension-deformation law (Evans, 1973*b*)

$$T_x = \frac{\mu}{2}(\lambda_x^2 - \lambda_x^{-2}) \tag{1}$$

where T_x is the membrane tension acting in the x direction, λ_x is the extension ratio (final length divided by initial length) and μ is an elastic constant which is a shear modulus of elasticity.

As Eq. 1 demonstrates, in order to measure an elastic constant, a known tension (force/width) must be exerted on the membrane, and the extension ratio (length/original length) must be measured, or vice-versa. The direct experiment on a membrane strip as illustrated in Fig. 2 is impossible to perform (because of the small sizes and forces involved). Consequently, we use two "micro-force" techniques, shown in Fig. 3, to deform intact red cells in a well-defined way: (1) a portion of cell membrane is sucked into a small micropipette (internal diameter $\leqq 1$ μm) such that a decrease in pressure causes the "tongue" of the membrane to extend further into the pipette (Evans, 1973*b*; Evans & LaCelle, 1975); (2) cells adhering to the surface of a parallel-plate flow channel are elongated by a fluid shear force (Hochmuth & Mohandas, 1972; Hochmuth *et al.*, 1973).

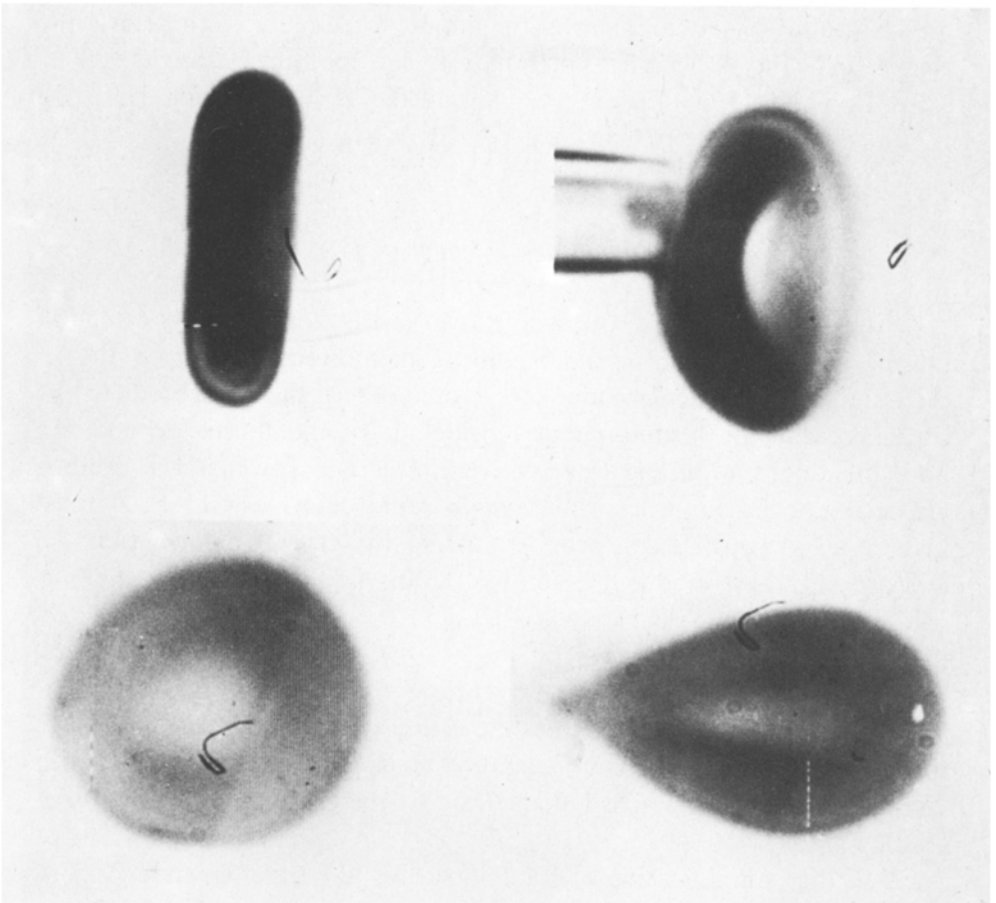

Fig. 3. Photographs of videotape recordings of the two micro-force experiments used in determining red cell membrane mechanical properties. (*a*) and (*b*) show a single cell in the micropipette suction experiment. (*c*) and (*d*) show a single cell in the fluid shear deformation experiment. (*a*) and (*c*) show the cell in its undeformed, biconcave shape, while (*b*) and (*d*) show it in its deformed state. The cell diameters are about 8 μm

Evans (1973*b*) has analyzed both the deformation produced by micropipette suction of membrane "tongues" and the fluid shear deformation of point-attached red cells using the hyperelastic constitutive relation, Eq. 1, for the deformation of a membrane "strip". In both cases, the material was first order (described as in Eq. 1) and the *intrinsic material elastic constant* μ obtained from each experiment was the same, with a value of approximately 10^{-5} N/m (10^{-2} dyne/cm). Subsequent studies have confirmed this value for the constant

$$\mu = 1 \times 10^{-5} \text{ N/m} \quad (1 \times 10^{-2} \text{ dyne/cm}).$$

This value for μ demonstrates the minute force required to deform the elastic strip (Fig. 2) from a 1 μm square to a $1/2 \times 2$ μm rectangle ($\lambda_x = 2$). Thus, from Eq. 1, $T_x = 1.9 \times 10^{-5}$ N/m and the force, F_x, acting along the 1/2 μm side is $F_x = 9 \times 10^{-12}$ N (e.g., 9×10^{-13} Kg).

Membrane Viscoelasticity

Now, suppose we take the strip shown in Fig. 2 and rapidly extend it. During rapid elongation, the *measured* membrane tension in the x-direction at any particular value of λ_x would exceed the value predicted by Eq. 2, because the instantaneous tension in the membrane depends on both the deformation and the *rate of deformation.* The material exhibits viscoelastic behavior when subjected to rapid deformations; Eq. 1 must include a "viscous" term, proportional to the rate of deformation. To first order, Eq. 1 is modified as follows (Evans & Hochmuth, 1976*a*)

$$T_x = \frac{\mu}{2}(\lambda_x^2 - \lambda_x^{-2}) + 4\eta \frac{\dot{\lambda}_x}{\lambda_x} \tag{2}$$

where the "dot" above λ_x denotes the ordinary derivative with respect to time. The constant of proportionality, η, is a two-dimensional shear viscosity or "surface viscosity" intrinsic to the membrane in the viscoelastic region.

A further simplification of Eq. 1 illustrates the time dependence. The strip (Fig. 2) is slowly extended to a specific extension ratio $\bar{\lambda}_x$ and then released (T_x is set equal to zero). Direct integration of Eq. (2) (with $T_x = 0$) predicts the decrease in the extension ratio λ_x with time t. The time required for the strip to "relax" to a length which is just half way between its original (stretched) and final (unstretched) length is

$$t_{0.5} \approx \eta/\mu \tag{3}$$

for $\bar{\lambda}_x \sim 2$. Since the value for μ is known from our elasticity experiments, we can measure a value for $t_{0.5}$ and use Eq. 3 to calculate the surface viscosity η.

In the actual experimental study of the viscoelastic relaxation of red cell membrane, a projection or "bump" from a human red blood cell is sucked into a micropipette (with internal diameter $\leqq 1$ μm) and held there for a few seconds. Then the cell is gently, but rapidly, expelled from the end of the pipette and the time required for the projection to relax to half of its initial length (the length along the axis of the pipette) is measured.

As above, we call this time the "$t_{0.5}$". Our analysis of the bump relaxation (Evans & Hochmuth, 1976*a*) indicates that for a wide range of initial bump lengths,

$$t_{0.5} = 3\,\eta/\mu. \tag{4}$$

The measured value for $t_{0.5}$ is about 0.3 sec (Evans & Hochmuth, 1976*a*). Therefore, Eq. 4 gives the shear viscosity parameter,

$$\eta \approx 1 \times 10^{-6} \text{ N-sec/m} \quad (1 \times 10^{-3} \text{ poise} \cdot \text{cm}).$$

Membrane Viscoplasticity

In this third example, we will produce a tension in the membrane which is sufficient to permanently, i.e., plastically, deform it; the membrane will not return to its original shape when the tension is removed. Therefore, *at least* two intrinsic membrane constants are required to describe the phenomenon of plastic deformation (Bingham, 1922): (1) a yield shear; (2) a "plastic" shear viscosity. The applied force resultants that create membrane shear must exceed the yield shear before plastic deformation can take place. Once the yield shear is exceeded, the "plastic viscosity" characterizes the *rate* at which the membrane undergoes irreversible deformation. This classical two-parameter theory has been used to describe the rate of deformation of a three-dimensional viscoplastic material in simple shear (Bingham, 1922; Prager, 1961). Recently, we specialized the general theory of Hohenemser and Prager (Prager, 1961) to the plastic deformation of a two-dimensional membrane. The first order "constitutive equation" is given by

$$\begin{aligned} &\dot{\lambda}_x = 0, && T_s < T_0, \\ &T_s - T_0 = 2\,\eta_p \frac{\dot{\lambda}_x}{\lambda_x}, && T_s > T_0, \end{aligned} \tag{5}$$

where T_s is the maximum shear resultant in the membrane and η_p and T_0 are the intrinsic material constants – the plastic shear viscosity and yield shear, respectively. When the maximum shear resultant is less than the yield shear, the rate of plastic deformation is zero, i.e., the material behaves recoverably. When the shear resultant exceeds the yield shear, the rate of plastic deformation is proportional to the difference between the shear resultant and the yield shear, T_0. The membrane shear resultant is simply the mean deviation between the principal tensions. For uniaxial tension,

$$T_s = \frac{T_x}{2}. \tag{6}$$

Eqs. 5 and 6 specify the plastic deformation of the membrane strip in Fig. 2:

$$\begin{aligned} &\lambda_x = 0, && \frac{T_x}{2} < T_0, \\ &\frac{T_x}{2} - T_0 = 2\eta_p \frac{\dot{\lambda}_x}{\lambda_x}, && \frac{T_x}{2} > T_0. \end{aligned} \tag{7}$$

In this third experiment, we slowly extend the element to the point where, upon removal of T_x, the rectangular strip no longer returns to its initial square shape (the membrane commences plastic deformation). We have reached the maximum elastic extension ratio, $\lambda_x = \hat{\lambda}_x$. The initial part of the experiment gives two independent ways to obtain a value for the yield shear T_0: (1) direct measurement of the value of T_s when plastic flow begins ($T_0 = T_s = T_x/2$); (2) calculate the yield shear from Eq. 1 using the maximum elastic extension ratio $\hat{\lambda}_x$, and $T_0 = T_x/2$. After determining the yield shear, we increase the membrane tension T_x to some value in excess of $2T_0$ and observe the *time dependent* plastic *deformation* of the strip. Integration of Eq. 7 gives an exponential growth of the element with time:

$$\lambda_x/\hat{\lambda}_x = \exp\left\{\left(\frac{T_x - 2T_0}{4\eta_p}\right) t\right\}. \tag{8}$$

The "plastic" surface viscosity governs the logarithmic growth of the element extension *vs.* time for specific membrane tensions.

Both micro-force techniques have been applied to the study of membrane viscoplasticity. Either technique can be used to determine a value for T_0. However, a value for η_p can only be determined from the rate of plastic deformation of point-attached red cells deformed by an extracellular fluid shear stress (Fig. 4).

Evans and LaCelle (1975) reported that departure from elastic behavior appeared rapidly for maximum extension ratios greater than approximately 3:1 in micropipette suction experiments. Thus, we can estimate the yield shear from Eq. 1 by noting that when $\lambda_x = \hat{\lambda}_x = 3$, $T_x = 2T_0$ and

$$T_0 = \frac{\mu}{4}(\hat{\lambda}_x^2 - \hat{\lambda}_x^{-2}) \simeq 2.0 \times 10^{-5}\ \text{N/m}\ (2.0 \times 10^{-2}\ \text{dyne/cm}). \tag{9}$$

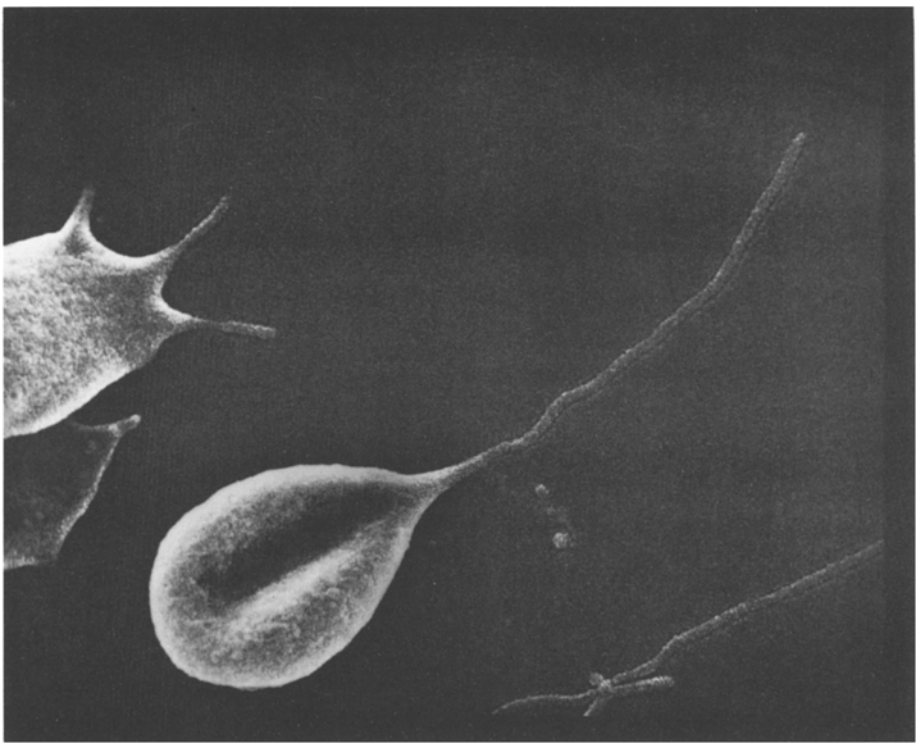

Fig. 4. A red cell membrane tether "plastically" pulled from a point-attached red cell by a fluid shear force. (*See* Hochmuth *et al.* (1973) for procedure.) This scanning electronmicrograph was kindly furnished by Dr. J.R. Williamson, Department of Pathology, Washington University

Hochmuth *et al.* (1973) and Williamson, Shanahan & Hochmuth (1975) have measured the plastic growth of "microtethers" (membrane filaments or strands) pulled from point-attached red cells under the action of fluid shear stresses (Fig. 4). The "critical" fluid shear stress required to hold the tether at a fixed length has been measured to be approximately $0.15\,\mathrm{N/m^2}$. The yield shear, T_0, is calculated from the measurement of the critical fluid shear stress using a simple "force balance" on the red cell and the tether:

$$F_{\text{cell}} = F_{\text{tether}} = \tau_{\text{crit}} \cdot A = T_x \cdot 2\pi r_t = 2T_0 \cdot 2\pi r_t,$$

or

$$T_0 = \tau_{\text{crit}} A/4\pi r_t \tag{10}$$

where F denotes force, τ_{crit} is the critical extracellular fluid shear stress, A is the cell area in contact with the flowing fluid (approximately $70\,\mu\mathrm{m}^2$) and r_t is the tether radius ($2\pi r_t$ is the circumference) corresponding to

the structural material that resists shear deformation. From observation, the outer tether diameter is approximately 0.1 μm. However, it is probable that the material undergoing plastic deformation is located on the cytoplasmic surface of the tether (membrane) and a reasonable value for r_t would be 0.045 μm. Thus, Eq. 10 gives

$$T_0 = 1.8 \times 10^{-5} \text{ N/m} \quad (1.8 \times 10^{-2} \text{ dyne/cm}). \tag{11}$$

for $\tau_{crit} = 0.15$ N/m^2, $A = 70$ μm^2, and $r_t = 0.045$ μm. The values for T_0 determined by the micropipette suction experiment and the tether experiment are in agreement (*compare* Eq. 9 with Eq. 11).

We have performed an analysis (Evans & Hochmuth, 1976*b*) of tether growth experiments (Hochmuth *et al.*, 1973; Williamson *et al.*, 1975) to determine a value for η_p (the viscoplastic viscosity), using the viscoplastic constitutive relation (Eq. 5). Briefly, the results of the analysis show that

$$\eta_p = \frac{\tau_{crit} A}{8\pi} \cdot \frac{G_t}{\dot{L}} \tag{12}$$

where $\dot{L}$ is the tether growth rate and G_t is a "tether growth parameter" (from analysis), which is only a function of the ratio of the fluid shear stress, τ, (imposed on the cell during tether growth) to the critical fluid shear stress, τ_{crit}. The tether radius does not enter into the calculation of η_p. From the data of Hochmuth *et al.* (1973):

$$3 \times 10^{-8} \leqq \dot{L} \leqq 2 \times 10^{-7} \text{ m/sec}$$

when

$$1.3 \leqq \tau/\tau_{crit} \leqq 2.3.$$

For this range of τ/τ_{crit}, the theoretical result (Evans & Hochmuth, 1976*b*) is $0.7 \leqq G_t \leqq 4.9$. Thus,

$$G_t/\dot{L} = \text{constant} \simeq 2.4 \times 10^7 \text{ sec/m}.$$

The substitution of this value for $G_t/\dot{L}$ into Eq. 12 along with $\tau_{crit} = 0.15$ N/m^2 and $A = 70$ μm^2 yields

$$\eta_p = 1 \times 10^{-5} \text{ N-sec/m} \quad (10^{-2} \text{ poise} \cdot \text{cm}).$$

Discussion

Measured values of the four intrinsic material constants of the human red cell membrane are summarized in Table 1. Now, what do the values in Table 1 tell us about the membrane composition?

Consider the four material constants for the lipid bilayer component of the membrane. First of all, the shear modulus μ and yield shear T_0 are *zero* for a lipid bilayer. It is a liquid in two dimensions and can not sustain any membrane shear resultant without "flow". The lipid bilayer resists area dilation (isotropic tension) because of the interfacial free energy required to "expose" the hydrophobic interior of the membrane. The lipid bilayer also opposes rate of deformation and has surface viscosity. The published values for lipid viscosity (*see*, for example, Edidin, 1974) are given between 1 and 10 poise (0.1 and 1 N-sec/m^2). Multiplying these numbers by a membrane thickness of 10^{-8} m provides a "pseudo" property conversion to give surface viscosities of order $10^{-9} - 10^{-8}$ N-sec/m – two to four orders of magnitude less than the values for the surface viscosity of red cell membrane given in Table 1. However, there is no inconsistency between the measured, lipid bilayer characteristics and the red cell membrane properties presented in Table 1. Our experiments assess the sum *total* of the membrane's mechanical behavior. Clearly, we are investigating a structural component or "matrix". From the relative values of material properties, it is apparent that the lipid bilayer is simply "along for the ride" when the membrane is deformed; the lipid bilayer acts like a two-dimensional "liquid sealer" for this "matrix" as shown in Fig. 1. Thus, our measurements are specific to the structural component of the *intact* red cell membrane and give a way of investigating this component *in situ*.

Table 1. Summary of values for intrinsic material constants for human red cell membrane in shear at room temperature[a]

	Shear modulus of elasticity μ(N/m)	Shear viscosity in the elastic domain: η(N-sec/m)	Yield shear: T_0(N/m)	Shear viscosity in the plastic domain: η_p(N-sec/m)
Micropipette Suction	10^{-5} (1, 2)[b]	10^{-6} (5)[b]	2×10^{-5} (6)[b]	(not applicable)
Fluid shear Deformation	10^{-5} (1, 3, 4)[b]	(not applicable)	2×10^{-5} (6)[b]	1×10^{-5} (6, 7)[b]

[a] The references in which the values appeared are given in parenthesis and footnoted below. [Note that a shear modulus was given previously in the form of a three-dimensional modulus (Hochmuth & Mohandas, 1972; Hochmuth et al., 1973) with a value of 10^4 dyne/cm^2 (10^3 N/m^2) obtained by dividing the two-dimensional value of 10^{-5} N/m by an assumed membrane thickness of 10^{-8} m.]

[b] (1) Evans (1973*b*), (2) Evans & LaCelle (1975), (3) Hochmuth & Mohandas (1972), (4) Hochmuth *et al.* (1973), (5) Evans & Hochmuth (1976*a*), (6) Evans & Hochmuth (1976*b*), (7) Williamson *et al.* (1975).

We thank Dr. Williamson, Department of Pathology, Washington University for furnishing the photograph shown in Fig. 4.

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