ESTIMATION OF VISCOUS DISSIPATION INSIDE AN ERYTHROCYTE DURING ASPIRATIONAL ENTRY INTO A MICROPIPETTE

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ABSTRACT Viscous dissipation inside the erythrocyte during its aspirational entry into a micropipette is analyzed. The motion of the intracellular fluid is approximated by a flow into the micropipette orifice from a half space (the portion of the erythrocyte outside the micropipette). The stream function and intracellular pressure (p) in the half space are obtained as a function of radial and axial positions near the orifice. Solution of the boundary value problem for a uniform stream entering a circular hole gives $p = 2\eta_{\rm H}Q/\pi R_{\rm p}^3$, where $\eta_{\rm H}$ is the intracellular viscosity, Q is the total discharge, and $R_{\rm p}$ is the pipette radius. The results indicate that the moving erythrocyte membrane helps to drive the intracellular fluid into the orifice. For normal erythrocytes, p is only ~0.5% of the total aspiration pressure (ΔP) . The contribution of p to ΔP , however, may become significant when there is a large increase in $\eta_{\rm H}$ due to a markedly elevated intracellular hemoglobin concentration or an alteration of the physical state of hemoglobin.

INTRODUCTION

There have been considerable advances in studies on the viscoelastic properties of the red cell membrane (Evans and Skalak, 1980; Fung, 1981). With the use of the micropipette aspiration technique, the nonlinear viscoelastic response of the erythrocyte membrane has been investigated (Evans and Hochmuth, 1976; Chien et al., 1978; Tozeren et al., 1982). In these studies the deformation of a portion of an erythrocyte during aspirational entry into a micropipette was analyzed. The theoretical basis of their analysis is the approximation of the cell membrane as an infinite plane membrane undergoing deformations at constant surface area. The results of the experiments by Chien et al. (1978) imply the absence of any static frictional forces between the cell membrane and the pipette for short durations. However, to account for the energy dissipation they point out several sources of viscous losses: (a) the viscous behavior of the cell membrane, (b) Poiseuille flow in the pipette, (c) viscous flow in the thin lubrication layer between the cell membrane and the wall of the pipette, and (d) the flow of hemoglobin in the erythrocyte.

In this paper, the viscous dissipation inside the erythrocytes in micropipette experiments has been analyzed. The pattern of flow of the intracellular hemoglobin solution before and after entry into the pipette is quite different. For the portion of the erythrocyte already in the pipette, except for a short entry region, the hemoglobin moves like a rigid body with the cell membrane. For the portion of the erythrocyte outside the pipette, a creeping flow is set up in the hemoglobin solution by the application of the pressure difference and by the motion of the membrane. A first approximation to this motion is the flow into an orifice (the micropipette) from an half-space (the portion of the erythrocyte outside the pipette). This approximation is quite reasonable if two conditions are satisfied. (a) In the experiments, the radius of the pipette must be very small compared with the radius of the erythrocyte, and (b) in the orifice flow, contribution to viscous dissipation from regions outside a small vicinity of the orifice must be negligible. For uniform efflux velocities at the orifice, this condition is valid because the velocities approach zero very rapidly as radial distance from origin increases.

The governing equations of the orifice flow and proper boundary conditions are given in the Formulation section. Solutions for velocities and pressure are obtained in the Numerical Results section. A simple formula is developed to estimate the time constant due to fluid dissipation recently introduced by Tözeren et al. (1982). It is shown that this time constant is directly proportional to the viscosity of the hemoglobin $\eta_{\rm H}$ and the radius of the pipette $R_{\rm p}$, and decreases with the increasing initial elastic response of the membrane. These conclusions agree with those reported by Hochmuth et al. (1984) at a recent meeting.

FORMULATION

Consider the aspiration of an erythrocyte into a micropipette with radius R_p (Fig. 1). The cell membrane is assumed to be an infinite plane



FIGURE 1 Schematic drawing to show the aspiration of an erythrocyte into a micropipette.

membrane, a small portion of which is aspirated into the tube (see Tozeren et al., 1982). The deformations of the membrane are assumed to occur at constant surface area. Accordingly, the magnitude of the radial membrane velocity outside the pipette, V, which is directed toward the pipette axis, is

$$V = \frac{R_{\rm p}}{R} \dot{D}_{\rm p} \tag{1}$$

where D_p is the rate of displacement of the portion of the membrane aspirated into the pipette.

The motion in the erythrocyte is assumed to be a slow, steady flow of a viscous incompressible fluid (see Fig. 2). A first approximation to this motion is the flow into an orifice (the micropipette) from an half space (the portion of the erythrocyte outside the pipette). The inertial terms are neglected in the Navier-Stokes equations and introducing an axisymmetric stream function ψ , the equation governing the axisymmetric steady creeping flow through the orifice is obtained:

$$E^2 E^2 \psi = 0 \tag{2}$$

where the differential operator E^2 is

$$E^{2} = \frac{\partial^{2}}{\partial R^{2}} - \frac{1}{R}\frac{\partial}{\partial R} + \frac{\partial^{2}}{\partial z^{2}}$$
(3)

In terms of ψ , the velocity components are given as

$$v_{z} = \frac{1}{R} \frac{\partial \psi}{\partial R}, v_{R} = \frac{1}{R} \frac{\partial \psi}{\partial z}$$
 (4)



FIGURE 2 Flow of intracellular fluid through an orifice as the erythrocyte membrane is aspirated into the micropipette.

The velocities are subject to the following boundary conditions.

$$v_z = D_p, v_R = 0, \qquad \text{at } 0 < R < R_p \tag{5}$$

$$v_z = 0, v_R = \frac{R_p}{R} \dot{D}_p, \quad \text{at } R > R_p$$
 (6)

The boundary condition, Eq. 5, implies that axial velocities are uniform at the orifice. According to Eq. 6 the fluid at the boundary moves with the membrane undergoing deformations at constant surface area.

A general solution of Eq. 2 is given by Parmet and Saible (1965):

$$\psi = R \int_0^\infty A(t) J_1(Rt) e^{-zt} dt + zR \int_0^\infty B(t) J_1(Rt) e^{-zt} dt$$
(7)

where $J_1(Rt)$ is the Bessel function of first order, and A(t) and B(t) are unknown functions determined by the boundary conditions of Eqs. 5 and 6.

Another physical variable of interest is the pressure. Total pressure difference (applied aspiration pressure) ΔP is made up of two parts: (a) the pressure difference across the two faces of the membrane, and (b) the pressure drop in the fluid. The present paper is concerned with the determination of the pressure drop inside the erythrocyte, p.

An expression giving pressures in the fluid is found by integrating the following differential equations given by Happel and Brenner (1965):

$$\frac{\partial p}{\partial R} = -\frac{\eta_{\rm H}}{R}\frac{\partial}{\partial z}\left(E^2\psi\right), \frac{\partial p}{\partial z} = -\frac{\eta_{\rm H}}{R}\frac{\partial}{\partial R}\left(E^2\psi\right) \tag{8}$$

where $\eta_{\rm H}$ is the viscosity of the intracellular hemoglobin solution. Applying the differential operator E^2 to ψ given by Eq. 7, we obtain

$$E^{2}\psi = -2\int_{0}^{\infty} Rt B(t) J_{1}(Rt) e^{-tt} dt.$$
 (9)

Differentiating Eq. 9 gives

$$\frac{\partial p}{\partial R} = -2\eta_{\rm H} \int_0^\infty t^2 B(t) J_1(Rt) e^{-tt} dt$$
$$\frac{\partial p}{\partial z} = -2\eta_{\rm H} \int_0^\infty t^2 B(t) J_0(Rt) e^{-tt} dt \qquad (10)$$

where $J_0 R(t)$ is the Bessel function of zero order. The total pressure differential is

$$\mathrm{d}p = \frac{\partial p}{\partial R} \,\mathrm{d}R + \frac{\partial p}{\partial z} \,\mathrm{d}z\,. \tag{11}$$

Substitution of Eq. 10 into 11 and using

$$J_1(Rt)\mathrm{d}R = -\frac{1}{t}\frac{\mathrm{d}J_0(Rt)}{\mathrm{d}R}\mathrm{d}R,$$

$$e^{-zt}\mathrm{d}z=-\frac{1}{t}\frac{\mathrm{d}}{\mathrm{d}z}e^{-zt}\mathrm{d}z,$$

we obtain

$$\mathrm{d}p = 2\eta_{\mathrm{H}} \,\mathrm{d} \left[\int_0^\infty t \,B(t) \,J_0(Rt) \,e^{-zt} \mathrm{d}t \right] \tag{12}$$

Integrating from infinity to an arbitrary point (R, z):

$$p = 2\eta_{\rm H} \int_0^\infty t \ B(t) \ J_0(Rt) \ e^{-zt} {\rm d}t. \tag{13}$$

Velocities and pressure are determined as a superposition of solutions of

two boundary value problems: (a) uniform stream entering a circular hole with constant velocity D_p

$$v_{\rm R} = 0$$
, and
 $v_z = g(R) = \begin{cases} \dot{D}_{\rm p}, & 0 < R < R_{\rm p} \\ 0, & R > R_{\rm p} \end{cases}$, at $z = 0$ (14)

and (b) flow due to the radial motion of the membrane subject to constant area deformations:

v = 0 and

$$v_{\rm R} = f(R) = \begin{cases} 0, & 0 < R < R_{\rm p} \\ -R_{\rm p}\dot{D}_{\rm p}/R, & R > R_{\rm p} \end{cases}, \quad \text{at } z = 0. \tag{15}$$

As outlined in the Appendix, two sets of functions A(t) and B(t) are determined by using the boundary conditions (Eq. 14) and (Eq. 15), respectively. These functions are then substituted into Eq. 7 and 13 to obtain the solution of the present orifice problem. For the boundary value problem in (a) given by Eq. 14 we obtain:

$$\psi/(\dot{D}_{\rm p}R_{\rm p}) = \int_0^\infty J_1(Rt) J_1(R_{\rm p}t) \frac{e^{-zt}}{t} dt + Rz \int_0^\infty J_1(Rt) J_1(R_{\rm p}t) e^{-zt} dt \quad (17)$$

$$p/(\eta_{\rm H}\dot{D}_{\rm p}R_{\rm p}) = 2\int_0^\infty t J_1(R_{\rm p}t) J_0(Rt) e^{-zt} {\rm d}t$$
 (18)

and for the boundary value problem in (b) given by Eq. 15 we derive

$$\psi/(\dot{D}_{\rm p}R_{\rm p}) = -zR \int_0^\infty J_0(R_{\rm p}t) J_1(Rt) e^{-zt} zt$$
 (19)

$$p/(\eta_{\rm H}\dot{D}_{\rm p}R_{\rm p}) = -2\int_0^\infty t \,J_0(R_{\rm p}t)J_0(Rt)\,e^{-zt}{\rm d}t\,. \tag{20}$$

Note that the streamlines and the fluid pressure corresponding to orifice flow with boundary conditions given by Eqs. (5) and (6) are obtained by adding the solutions from Eqs. 17 and 19 and Eqs. 18 and 20, respectively.

NUMERICAL RESULTS

The values of pressure and stream function at some selected points can be obtained by numerical integration. The ψ and p presented in these figures are made dimensionless by dividing the dimensional variables by $D_p R_p^2$ and $\eta_H D_0/R_p$, respectively.

In the first boundary value problem given by Eq. 14, uniform efflux velocities are specified at the orifice (rigid body motion of the fluid starts upon the entry into the pipette). The velocities elsewhere on the boundary are zero. The second boundary value problem formulates the flow due to radial motion of the membrane in the half space. Radial and axial velocities are taken as zero at the orifice (no discharge into the pipette). Superposition of these solutions give the velocities and pressures for the flow in the erythrocytes. The results obtained by specifying uniform efflux velocities at the orifice are presented in Figs. 3-5. In Fig. 3 the streamlines are given for several values of ψ . Streamlines intersect the boundary perpendicularly giving zero radial velocities as specified by the boundary conditions. Consider the surface obtained by rotating a curve connecting a point on the z axis to a point on a streamline about z axis. The value of the stream function on this streamline times 2π , $2\pi\psi$, gives the discharge through this surface. For the uniform stream entering the orifice we have

$$2\pi\psi = \pi R^2 V$$
, at $z = 0, 0 < R/R_p < 1$. (21)

It can be seen from Fig. 3 that this relation holds in the present case.

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FIGURE 3 Streamlines for uniform efflux velocity at orifice.

Streamlines for a sink positioned at the origin are straight lines passing through the origin. Fig. 3 shows that the streamlines for flow into the orifice approach the streamlines for the sink, one or two tube radii away from the origin. This shows that the velocity distribution at the orifice has little effect on the flow at some distance from the origin. The total discharge determines flow variables at these points.

Isobar curves are given in Fig. 4. The pressure drop occurs mainly in



FIGURE 4 Isobar curves for uniform efflux velocity.



FIGURE 5 Pressure vs. R/R_p at several levels of $-z/R_p$.

the vicinity of the pipette orifice, where the major contribution of viscous dissipation takes place. Pressures are not constant at the orifice, as can be seen from this figure and Fig. 5. The average pressure at the orifice is slightly more negative than the pressure at the origin. Fig. 5 gives pressure vs. R/R_p curves for several values of z/R_p .

The solutions for the boundary conditions (in Eq. 15) are presented in Fig. 6. According to the boundary conditions, motion is created by the radial motion of the membrane, but no discharge is allowed into the pipette. Streamlines are close to each other near the boundary (higher velocities). Away from this source of momentum velocities fall down. This explains why the distances between streamlines increase at greater values of z. The streamline $\psi = 0.5$ gets as close as the point R = 2, z = 1 to the origin. This is equal to the total discharge driven into the pipette by the pressures in the first boundary value problem. This shows that a considerable amount of fluid is driven near the orifice by the radial motion of the membrane.

The solution of the boundary value problem (from Eq. 14) presented in Eqs. 17 and 18 gives a pressure drop between the origin and infinity as

$$p = \frac{2\eta_{\rm H}Q}{\pi R_{\rm p}^3} \tag{22}$$

where Q is the total discharge. The pressure drop between the origin and infinity corresponding to the boundary value problem of Eq. 15 can be shown to be equal to zero by analytical integration of Eq. 20. Hence, the



FIGURE 6 Streamlines for flow due to the radial motion of the membrane (boundary condition for Eq. 15).

pressure drop for the combined problem corresponding to Eq. 5 and 6 is also given by Eq. 22. Because $Q - \pi R_p^2 D_p$, Eq. 22 can be written as

$$p = \frac{2\eta_{\rm H} D_{\rm p}}{R_{\rm p}} \tag{23}$$

As shown in Fig. 5, p is not uniform in $0 < R < R_p$, and it has a peak value towards the edges.

Eq. 23 is simple and useful because it allows the estimation of the contribution of viscous cell dissipation to the suction pressure analytically as a function of the time rate of change of aspiration length. However Eq. 23 must be considered as a lower bound, because the presence of the opposing wall of the cell membrane is not taken into account in the present treatment. The presence of the cell contour may retard considerably the radial velocity component in the region near the pipette. Our computational results, based on the infinite fluid region bounded by a plane wall, indicate that radial velocity component decreases sharply in a spherical region of radius $2R_p$. Note that the shortest distance between the tip of the pipette and opposing membrane wall is $\sim 2.6R_n$ when R_n -0.5 µm. Numerical estimation of viscous dissipation inside an erythrocyte during aspiration into a micropipette by using the finite element method is presently under consideration. In such computations, the aspiration length and its time rate of change must be specified along with the cell contour. The results will allow us to assess how closely Eq. 23 describes cell dissipation during micropipette aspiration.

The solution of the orifice problem assuming constant pressures $(p - p_0 \text{ at } 0 < R < R_p)$ at the orifice is given by Happel and Brenner (1965). In this case a parabolic distribution of axial velocities is obtained: $v_z - V[1 - (R^2/R_p^2)]$ at $0 < R < R_p$. The pressure-discharge relation is

$$p_0 = \frac{3\eta_{\rm H}Q}{2R_{\rm p}^3} \,. \tag{24}$$

This shows that the present model, which takes into account the role of the moving membrane in driving fluid through the orifice, has a smaller coefficient, $2/\pi$ in Eq. 22, for p than the coefficient, 3/2 in Eq. 24, for p_0 . As a result, the average p value is lower than p_0 .

Finally, we compute the time constant τ_f introduced by Tözeren et al. (1982, Eq. 16) to account for the dissipation inside the erythrocytes.

$$\tau_{\rm f} = p / [2 {\rm A} \ G^*(0) \mu / R_{\rm p}] \tag{25}$$

where A is a parameter related to the rate of change of member area in the pipette, $A - (2\pi R_p D_p)/(\pi R_p^2) - 2D_p/R_p$, $G^*(0)$ is a material constant and μ is the shear modulus of elasticity of the membrane. Substitution into Eq. 25 and using Eq. 23 gives

$$\tau_{\rm f} = \frac{1}{2} \frac{\eta_{\rm H} R_{\rm p}}{G^*(0) \,\mu} \,. \tag{26}$$

Typical values for the physical variables involved in micropipette aspiration experiments are $\Delta P = 5 \text{ mm H}_20 = 480 \text{ dyn/cm}^2$, $R_p = 0.5 \mu \text{m}$ and $D_p = 10 \,\mu m/s$ (Chien et al., 1978). For normal human erythrocytes, $\eta_{\rm H} = 6 \times 10^{-2}$ dyn-s/cm² (Cokelet and Meiselman, 1968). Under these conditions, to drive the erythrocyte content into the pipette at a rate D_p , we need an applied pressures p of only 2.4 dyn/cm² according to Eq. 23. Comparison of this value of p with the pressure drop ($\Delta P = 480 \text{ dyn/cm}^2$) found experimentally shows that the contribution of viscous losses in the normal erythrocyte is negligible (~0.5% of total pressure drop) compared with losses due to other factors. Similarly, for this case, the time constant $\tau_{\rm f}$ computed by using Eq. 26 is ~0.35 ms ($\mu = 4.2 \times 10^{-3}$ dyn/cm, Chien et al., 1978). This value is much smaller than the time constant τ observed in actual experiments during the rapid phase of deformation (20 ms $\leq \tau \leq 100$ ms). This conclusion is in agreement with that reached in earlier estimations of the order of magnitude of the viscous losses inside the erythrocyte during micropipette aspiration (Evans and Hochmuth, 1976; Chien et al., 1978) and a recent quantitative analysis using a similar approach (Hochmuth et al., 1984).

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Although the present study indicates that intracellular viscous loss is negligible in comparison with membrane viscosity in micropipette aspiration for normal erythrocytes with a low $\eta_{\rm H}$, it may become a significant factor when $\eta_{\rm H}$ is elevated, e.g., following erythrocyte shrinkage in a hypertonic medium. Calculation based on Eq. 23 indicates that p would be 5-10% of ΔP when $\eta_{\rm H}$ is raised to 1 dyn-s/cm², which can be attained with a mean corpuscular hemoglobin concentration ($C_{\rm H}$) of ~44 g/dl or an osmolality of 480 m0sm (Sung and Chien, unpublished observations). For p to be one-half of ΔP , $\eta_{\rm H}$ needs be $\simeq 10$ dyn-s/cm², which can be attained when $C_{\rm H}$ is raised above 50 g/dl in a hypertonic medium of >600 mosM. Another condition in which the intracellular viscous dissipation can be important is where there is an alteration of the physiochemical state of the hemoglobin, e.g., when sickle cells are subjected to deoxygenation. In this case there is not only an increase of $\eta_{\rm H}$, but also the appearance of elastic behavior in the intracellular content as hemoglobin S undergoes gelation (Briehl, 1980; Chien et al., 1982).

In summary, several boundary value problems involving flow into an orifice from an half-space are considered as a model of flow in erythrocytes in micropipette experiments. It is found that the pressure drop between the origin and infinity substantially decreases if the motion of the membrane is taken into account. This shows that considerable amount of fluid is driven into the pipette by the motion of the membrane. According to the results, major contribution to viscous dissipation in orifice flows takes place in a small vicinity of the orifice. However, it is found that the dissipation inside normal erythrocytes is negligible compared to other sources of dissipation. The dissipation inside the cell would become significant when the intracellular fluid viscosity is raised to 1 dyn-s/cm² or higher.

APPENDIX

Computation of the Velocities and Pressure

In this section, velocities and pressure are determined as a superposition of solutions of two boundary value problems: (a) uniform stream entering a circular hole with constant velocity $\dot{D}_{\rm p}$

$$v_{\rm R} = 0$$
, and
 $v_{\rm z} = g(R) = \begin{cases} \dot{D}_{\rm p}, & 0 < R < R_{\rm p} \\ 0, & R > R_{\rm p} \end{cases}$, at $z = 0$ (A1)

and (b) flow due to the radial motion of the membrane subject to constant area deformations

$$v_z = 0$$
, and

$$v_{\rm R} = f(R) = \begin{cases} 0, & 0 < R < R_{\rm p} \\ -R_{\rm p}\dot{D}_{\rm p},/R, & R > R_{\rm p} \end{cases}, \quad \text{at } z = 0. \quad (A2)$$

The general solution for velocities are obtained by taking proper derivatives of ψ according to Eq. 3. These are

$$v_{\rm R} = \int_0^\infty [B(t) - tA(t)] J_1(Rt) e^{-zt} dt$$

- $z \int_0^\infty t B(t) J_1(Rt) e^{-zt} dt$ and
 $v_z = \int_0^\infty t A(t) J_0(Rt) e^{-zt} dt$
+ $z \int_0^\infty t B(t) J_1(Rt) e^{-zt} dt.$ (A3)

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At z = 0 (at the boundary) these expressions reduce into

$$v_{\mathsf{R}} = \int_0^\infty [B(t) - tA(t)] J_1(Rt) \, \mathrm{d}t, \quad \text{and}$$
$$v_z = \int_0^\infty tA(t) J_0(Rt) \, \mathrm{d}t. \tag{A4}$$

Consider (a) uniform efflux velocities (boundary conditions in Eq. A1). According to Eq. A4 and $v_{\rm R} = 0$ at z = 0, B(t) = tA(t) and A(t) is the Hankel transform of g(R):

$$g(R) = \int_0^\infty t J_0(Rt) A(t) dt.$$

The inverse transform gives

$$A(t) = \int_0^\infty R J_0(Rt) g(R) \,\mathrm{d}R. \tag{A5}$$

Substituting g(R) from Eq. A1 and integrating

$$A(t) = \dot{D}_{p}R_{p}\frac{1}{t}J_{1}(R_{p}t).$$
 (A6)

Using this form of A(t), ψ and p become

$$\psi/(\dot{D}_{p}R_{p}) = R_{0} \int_{0}^{\infty} J_{1}(Rt) J_{1}(R_{p}t) \frac{e^{-zt}}{t} dt + Rz \int_{0}^{\infty} J_{1}(Rt) J_{1}(R_{p}t) e^{-zt} dt \quad (A7)$$

$$p/(\eta_{\rm H}\dot{D}_{\rm p}R_{\rm p}) = 2\int_0^\infty t J_1(R_{\rm p}t) J_0(Rt) e^{-zt} \,\mathrm{d}t.$$
 (A8)

If radial velocities are specified as the boundary condition of Eq. A2, from Eq. A4 and $v_z = 0$ at z = 0, we have A(t) = 0 and $V_R = \int_0^\infty B(t) J_1(Rt) dt$, at z = 0. At z = 0 (the boundary) v_R is given by Eq. A2. Therefore, B(t)/t must be the Hankel transform of f(R):

$$f(R) = \int_0^\infty t J_1(Rt) \left[\frac{1}{t} B(t)\right] dt$$
 (A9)

and the inverse transform gives

$$B(t)/t = \int_0^\infty R J_1(Rt) f(R) dR$$

= $-R_p \dot{D}_p \int_{R_p}^\infty J_0(Rt) dR = \frac{R_p \dot{D}_p}{t} J_0(R_p t).$ (A10)

This choice of A(t) and B(t) yields

$$\psi/(\dot{D}_{p}R_{p}) = -zR \int_{0}^{\infty} J_{0}(R_{p}t) J_{1}(Rt) e^{-zt} dt$$
 (A11)

$$p/(\eta_{\rm H}\dot{D}_{\rm p}R_{\rm p}) = -2\int_0^\infty t J_0(R_{\rm p}t) J_0(Rt) e^{-tt} {\rm d}t.$$
 (A12)

The definite integrals Eqs. A7, A8, A11, A12 are numerically integrated to give stream function and pressures at some selected points. The results are given in Fig. 2-6.

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