

Rheology of Blood

EDWARD W. MERRILL

*Department of Chemical Engineering, Massachusetts Institute of Technology,
Cambridge, Massachusetts*

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I. RHEOLOGY

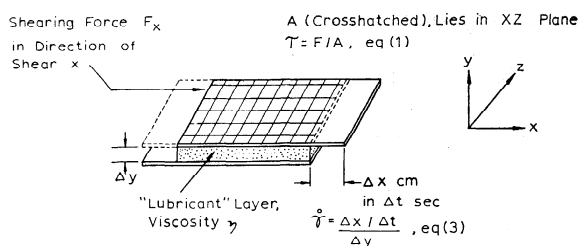
Rheology is a specialized part of fluid mechanics and is concerned principally with non-Newtonian and viscoelastic substances.

A Newtonian liquid is one in which the viscosity, at fixed temperature and pressure, is independent of the shear stress. Thus, a non-Newtonian liquid is one in which the viscosity depends on shear stress. Water and honey are Newtonian, but many aqueous suspensions of fine particulate matter such as water-base paint, plaster, and oil emulsions are non-Newtonian. The distinction is qualitatively obvious if one imagines two spoons, one in a pot of honey (Newtonian) and the other in a pot of mayonnaise (non-Newtonian emulsion). The honey is harder to stir (has a higher viscosity) than the mayonnaise, but when the spoons are removed

and held above the pots, the honey continues to drizzle off its spoon, whereas the mayonnaise coating the other spoon clings indefinitely to it without flow, thus exhibiting "infinite" viscosity.

Viscoelastic substances are those that show a capacity to recover original shape after a briefly applied stress, but flow after long periods of stress. Examples are rubber adhesives for joining paper, "bouncing putty," chewing gum, food-stuffs (bread dough), and all natural and synthetic rubber prior to vulcanization. To a very slight extent blood displays viscoelasticity, but from the rheological point of view, its non-Newtonian quality is far more significant.

To visualize the physics underlying viscosity, consider a freshly shuffled clean deck of cards placed on a table. If the top of the deck were gently pushed horizontally, the cards would tend to slide over each other more or less uniformly, "lubricated" by a thin film of air between each pair of card surfaces. If the cards were coated with a thin film of honey, it would require much more "push," horizontally applied, to make the deck slide apart.



PLAYING CARD VISCOMETER

Any two adjacent playing cards form an elementary device for measuring viscosity. Between the cards one could fix the film thickness Δy (cm) of the "lubricant" layer, whatever the composition might be; one could measure the force F (dynes) applied horizontally to the upper card causing it to move over the lower card; and one could determine the linear displacement Δx (cm) of one card relative to the other in a time interval Δt (sec), thus obtaining the rate of displacement $\dot{x}$ (cm/sec).

The overlap surface area of the lubricant film contained between both cards is A (cm²). The shear stress τ on the lubricant (shear force per unit area) is:

$$\tau = \frac{F}{A} \text{ (dynes/cm}^2\text{)} \quad (1)$$

The strain produced in the lubricant would be:

$$\gamma = \frac{\Delta x}{\Delta y} \text{ (dimensionless)} \quad (2)$$

and the strain rate (shear strain rate, *velocity gradient*¹) would be:

$$\dot{\gamma} = \frac{\Delta x}{\Delta t \Delta y} = \frac{\dot{x}}{\Delta y} \text{ (sec}^{-1}\text{)} \quad (3)$$

¹ Velocity gradient = rate of change of velocity in the direction x of shear stress with respect to distance normal to the plane of shear. Generally, velocity gradient = dV_x/dy , if y is the direction normal to the plane of shear.

The coefficient of viscosity, η , is by definition:

$$\eta = \tau/\dot{\gamma}(\text{dynes-sec})/\text{cm}^2(\text{poise}) \quad (4)$$

Compare the equation defining the shear modulus of elasticity G

$$G = \tau/\gamma(\text{dynes/cm}^2) \quad (5)$$

For Newtonian fluids (including all gases), the value of η in *equation 4* is independent of τ or $\dot{\gamma}$. For non-Newtonian liquids, η can vary with τ or $\dot{\gamma}$ over limited or extensive ranges and by small percentages or over decades (22). A special problem is posed with blood because it exhibits a "yield stress." This means that, if in the playing card experiment, one increases from zero the stress, but keeps it less than a critical value, the response will be elastic, following *equation 5* and not *4*, and on removal of the stress, the shape of the blood film will be unaltered, i.e., no flow will have occurred. However, if the yield stress is exceeded, irreversible deformation will occur.

House paint is an industrial liquid specifically designed to have yield stress, without which the applied wet film would sag and drool, like varnish, unless brushed out thinly. The yield stress of house paint prevents its flow vertically downward under gravitational stress.

The existence of yield stress means that, in *equation 4*, η can go to infinity since τ remains finite as the strain rate goes to zero. Conceptually, this is misleading (27) and it is more meaningful either to describe the non-Newtonian viscosity of blood in terms of a relationship of stress to strain rate or to cite the value of yield stress of blood and the limiting (minimum) viscosity attained at sufficiently high shear stress and shear rate, as discussed below.

In summary, the phrase blood rheology implies that blood exhibits a variable viscosity depending on how rapidly it is forced to flow under shear. Viscosity is defined as a ratio of shear stress to strain rate. An easily visualized, though somewhat impractical, means for quantitatively measuring these parameters has been suggested, and the meaning of yield stress has been considered.

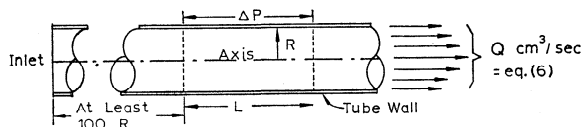
II. EXPERIMENTAL METHODS

A. Poiseuillian Devices

Because of its experimental simplicity, the capillary viscometer was first to come into general use and is still preferred for measuring the viscosity of a *Newtonian* fluid. The French physician Poiseuille (34) was the first to relate the viscosity of the liquid flowing in the capillary to what is measured experimentally; his motivation was understanding the circulation of blood. His attempts to carry out the capillary experiment on blood were thwarted for a variety of reasons, principally thrombogenesis, and he was forced to study simple liquids instead, such as saline solution. In any case, he set forth the relation bearing his name for steady laminar flow of a fluid through a straight cylindrical tube:

$$Q = \pi \cdot \frac{\Delta P}{L} \cdot \frac{R^4}{8\eta} \quad (6)$$

where Q = flow rate, R = inner radius of tube, ΔP = pressure drop along the tube over a distance L , η = (coefficient of) viscosity, and $\pi = 3.1416 \dots$



POISEUILLE

Thus, Poiseuille's law (*eq. 6*) predicts, all other parameters being held constant, that: 1) the flow rate will be halved if viscosity is doubled; 2) the flow rate will be augmented 16-fold if the radius is doubled; and 3) the pressure drop will be doubled if the length is doubled.

Equation 6 is derived from the requirement that in steady, well-developed² flow through a straight tube of constant cross section, the shear stress τ varies linearly with radial distance from the axis r , at any cross section, according to the equation:

$$\tau = \frac{\Delta P}{L} \cdot \frac{r}{2} \quad (7)$$

If the fluid is Newtonian and the flow is laminar (not turbulent), *equation 4* gives (for constant η) the result that the *local velocity gradient* (strain rate) must vary as:

$$\dot{\gamma} = dV/dr = (\Delta P/L) (r/2\eta) \quad (8)$$

i.e., also linearly from zero at the axis to a maximum value at the wall ($r = R$).

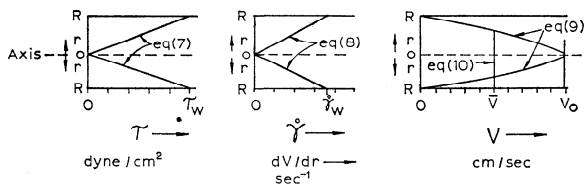
Manipulation of *equation 7*, η being constant, then leads to the well-known requirement that the velocity profile across the tube be parabolic, i.e.,

$$V/V_0 = 1 - \frac{r^2}{R^2} \quad (9)$$

and that the average velocity $\bar{V}$ is then given by the relation:

$$\bar{V} = V_0/2 \quad (10)$$

where $\bar{V} = \frac{Q}{\pi R^2}$ and V_0 = velocity at the tube axis.

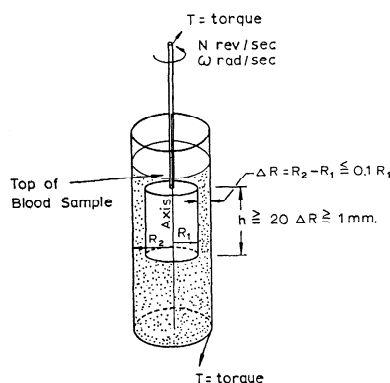


It is entirely possible to utilize a capillary viscometer for studying non-Newtonian liquids by modifying the manner in which the strain rate (velocity

² Well-developed means, practically speaking, after a tube length equivalent to 100 tube radii downstream from the entrance of the tube. At the entrance, and indeed at the exit, other pressure differences arise due to kinetic energy changes (acceleration or deceleration). Thus, the pressure drop ΔP ideally should be measured by pressure taps located a distance L apart but well removed from the entrance.

gradient) at the wall is calculated (16), but the principal difficulty is that the capillary viscometer is not suited to making measurements at a *low* rate of strain (or stresses), at least using conventional designs in which the liquid is driven through the tube by its own hydrostatic pressure. This disadvantage can be obviated, at the cost of complexity of design, by the use of diaphragm-type pressure transducers (3, 23).

Measurements of the viscous properties of non-Newtonian fluids at low rates of strain (low stresses) are better accomplished in viscometers derived from the concept of the sliding playing cards in which the fluid is contained between two radially symmetrical coaxial elements, one of which rotates relative to the other. The basic parameters measured are torque and rotational speed. The most common types are: 1) coaxial cylinder (Couette) viscometer, 2) cone-in-cone viscometer, and 3) cone-on-plate viscometer. For reasons shown subsequently, the coaxial cylinder arrangement is preferred for blood rheology, provided that: 1) the annular gap between cylinders is of the order of 1 mm or more; 2) the annular gap is 10% or less of the radius of either cylinder; 3) the length of the cylindrical surfaces is at least 20-fold greater than the annular gap; and 4) above and below the cylindrical surfaces the clearance is significantly greater, so that the stress developed in the fluid elsewhere than in the coaxial cylindrical gap contributes negligibly to the torque.



Under these conditions, the shear stress τ can be accurately obtained by measurement of torque T :

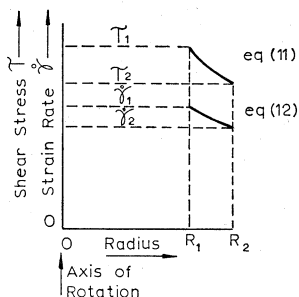
$$\tau_1 = \frac{T}{2\pi R_1^2 h} \quad (11)$$

(2) (2)

where subscript 1 refers to inner cylinder radius, subscript 2 refers to outer cylinder radius, h = height of vertical surface, R = radius, and T = torque. The corresponding strain rate (velocity gradient) is obtained as:

$$\dot{\gamma}_1 = \frac{2\omega R_2^2}{(R_2^2 - R_1^2)}; \quad \dot{\gamma}_2 = \frac{2\omega R_1^2}{(R_2^2 - R_1^2)} \quad (12)$$

where ω = angular velocity (radians/sec = $2\pi N$) and N = revolutions per second.



If desired the viscosity can be obtained as the ratio of *equation 11* to *equation 12*. Since in some devices the torque is measured on the external cylinder (2), whereas in others it is measured on the internal cylinder (1), one must evaluate the strain rate on the same cylinder as that which measures the torque.

III. ARTIFACTS AND BLOOD RHEOLOGY

Since Poiseuille's time, blood rheology has proved not only experimentally difficult but indeed peculiarly beset with artifacts. The artifacts in turn have led to inaccurate interpretations or to downright misleading conclusions.

To understand how the artifacts enter the picture, it is fruitful to "synthesize" blood starting with water, adding successively microions,³ proteins, lipids, and then the formed elements. At each step the artifacts reported or presumed are considered.

A. Pure Water

Pure (conductivity) water is difficult to test in capillary viscometers (i.e., to calibrate the capillary by water) that depend on hydrostatic pressure to drive the liquid because its surface tension, at 72 dynes/cm, can significantly change the efflux patterns from the capillary as well as the shape of the falling meniscus compared to pure organic liquids (alcohol, benzene, etc.) with smaller surface tension. It is also experimentally difficult to use pure water as a calibrating liquid in a Couette viscometer because of the slow dissipation of electrostatic charge that may render the viscometer an undesired electrometer.

B. Physiological Saline, Ringer Solution

The addition of microionic³ electrolytes (NaCl, CaCl₂, bicarbonate, phosphate, etc.) to water in the concentration relevant to blood greatly improves the

³ "Micro" in contrast to "macro" as represented by polyelectrolytes such as sodium polystyrene sulfonate, sodium polyacrylate, DNA, etc.

precision with which the Couette viscometer, properly designed, can be read, owing to dissipation of electrostatic charge that may form on the cylindrical surfaces. The absolute viscosities of such solutions are always Newtonian, lie a few percent above the viscosity of pure water at the same temperature, and are well documented. Thus such solutions make excellent reference standards for Couette and cone-on-plate viscometers. Because electrolytic solutions also make excellent corrosion media, choice of metals becomes important. Usually the stainless steels are adequate. Tantalum is the best of all materials in respect to anticorrosion properties but is difficult to machine. It is obvious that if a particular Couette or cone-on-plate viscometer indicates the saline solution to be non-Newtonian the viscometric reading is at fault. An apparent increase of viscosity with increase in rotational speed often indicates development of secondary flows (indicating that a more narrow gap is required); the converse may indicate bearing friction or some related mechanical problem. Any bubbles adherent to either surface of a coaxial (rotational) viscometer in general invalidate the reading. The electrical conductivity of physiological saline and similar solutions does nothing to help the several end-effect problems of capillary viscometers that operate by drainage under hydrostatic pressure.

C. Saline Solutions of Fractionated Plasma Proteins

Inasmuch as the plasma proteins are capable of denaturation at interfaces between their solution and a gas or a containing wall, two artifacts can arise in gravity-draining capillary viscometers, viz., decrease of effective capillary radius by sorption of the protein (cf. eq. 6) and change of shape of the menisci above and below the capillary; hence, change of the driving pressure gradient and of the kinetic energy corrections. However, solutions of a single protein (e.g., albumin and saline, γ -globulin in saline) may be relatively stable over a short period of time so that a viscometric determination can be accomplished.

D. Plasma and Serum

Anticoagulated or native plasma, especially, and serum usually present some form of experimental artifact in viscometry, attributable to a tendency toward rigid or semirigid surface films (14). In capillary viscometers the surface film is often sufficient to prevent, or grossly delay, passage of the liquid. In rotational viscometers the effect becomes particularly important in measurements conducted at low rates of strain (7, 14). Nevertheless, when the rotational viscometer is operated with a guard ring (which eliminates the interface) or when a capillary viscometer is operated such that flow rate is the imposed parameter (23) and pressure gradient (measured by transducer in a gas-free circuit) is the observed response, plasma and serum are Newtonian, down to zero strain rate and up to at least several thousand inverse seconds of strain rate.

Precisely which chemical species in plasma or serum are responsible for these

effects at the plasma-gas interface have not yet been documented, but free lipids (e.g., fatty acid) and lipoproteins are suspected. The effects are not confined to gas-liquid (e.g., air-liquid) interfaces. Hydrophobic surfaces, like silicone rubber, after contact with plasma rapidly become wettable by aqueous solutions (contact angle approaches zero) and are found to possess a film of bound protein (18). Blood oxygenators in which there is direct contact between air and blood produce a sludge having a high content of lipid and protein. Plasma obtained by clean venopuncture followed by immediate centrifugation in siliconized tubes has been shown to possess a much more striking tendency to form a rigid film at a gas interface than anticoagulated plasma. It is not evident what processes are involved that account for the diminished, though still pronounced, ability of stored anticoagulated blood (heparin, ACD, EDTA) to form rigid surface films.

E. Formed Elements and Physiological Saline or Equivalent

Usually the red cells so dominate rheological processes by reason of their volume concentration that the leukocytes and platelets are without observable effect. Furthermore, in many studies blood is centrifuged and the buffy coat (leukocytes and platelets) is removed prior to experimentation with the red cells.

When the red cells are washed to remove the plasma protein and then suspended in Ringer solution or physiological saline, at normal hematocrit levels (35-45), one obtains a rheologically simple, easily handled fluid, slow settling, not beset with unusual problems of surface film formation, and therefore attractive for study. Unfortunately, as will be shown, it bears little relation to the rheology of blood.

The principal artifact involved is that of the "Vand" (43) effect. In brief, according to this reasoning, there must be a layer next to the boundary surface in which the local concentration of suspended matter (cells or whatever) is lower than in the main body of the fluid because the centers of particles cannot physically be at the wall.

Visualize as the extreme limiting case a glass pipe 1.001 cm in diameter filled with glass marbles each 1.000 cm in diameter (i.e., stacked one on another). At the axis of the pipe the local volume fraction of marbles is 1.0 and at the wall, necessarily very close to zero. [The mean volume fraction would be a spherical volume inside a cylinder of height equal to the spheres' diameter, viz., $\left(\frac{\pi}{6} \cdot D^3\right) / \left(\frac{\pi}{4} \cdot D^2 D\right) = 2/3$.]

When the capillary diameter of a Poiseuillian viscometer approaches the diameter of a red cell (viz., 8 μ) one may expect the various complications of nonuniform concentration to ensue, but this is rarely the case in any rotational viscometer, except at the apex of a cone-on-plate viscometer.

What corrections are to be made in that case are not apparent. Models such as that of Vand are concerned with rigid, suspended bodies, whereas the red cell is easily deformed and distorted, so that its center of mass can approach the bound-

ary wall more closely than would be predicted from the model of a rigid, biconcave disc. The effect is easily noted in cinephotomicrography (2, 10).

The "wall-effect" problem is not to be dismissed lightly, for the microcirculatory vessels (arterioles, capillaries, venules) involve these geometrical considerations. The capillary in particular is a special problem in the fluid mechanical sense, since its lumen is the same or less than the diameter of the red cell. Passage of red cells through living capillaries of the microcirculation has only the most indirect connection with blood rheology. Strictly speaking, it is a microrheological problem: a process governed by membrane deformability and by surface chemistry (red cell/wall). In any case, except for the wall effect, the rheology of suspensions of red cells in physiological saline or equivalent solutions presents no grave problems of artifacts.

F. Whole Blood and Suspensions of Red Cells in Plasma

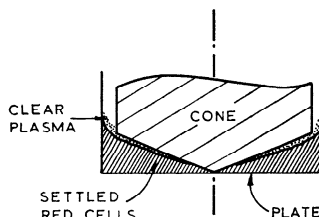
The measurement of the rheological properties of whole blood, or of red cells suspended in plasma, is complicated by the surface film effects of plasma by itself and by the wall effect of suspensions of red cells in saline. These effects are insignificant compared with those resulting from the interaction of plasma fibrinogen (*not* activated, i.e., *not* fibrin) with red cells.

Artifacts that derive from effects produced by fibrinogen and red cells are: 1) inconveniently rapid sedimentation of red cells, 2) syneresis of plasma next to any boundary surface, and 3) densification of the red cell core (increase in actual hematocrit).

Because of sedimentation, the cone-on-plate or cone-in-cone viscometer, when operated at low rotational speeds, is likely to be in error because of the existence of a plasma layer next to the upper coaxial surface (Fig. 1) regardless of whether it is on the upper or lower surface that the torque measurement is made. Since the fluid under shear is no longer homogenous, and since the plasma layer acts as a lubricant for the cell-rich fluid, the measured torque is substantially, but to an indefinite degree, less than it should be.

The coaxial cylinder viscometer is not quite so sensitive to red cell sedimentation as the conical viscometers, but since at low rates of strain ($< 1 \text{ sec}^{-1}$) the red cells can retract radially from the vertical cylindrical surfaces (Fig. 2), even in this configuration considerable pains must be taken to avoid the artifact of two-phase flow. For this reason, it is expedient to provide the viscometer cylinders with

FIG. 1. Schematic diagram of cone-on-plate viscometer, showing formation of clear plasma layer above a layer of red cells.



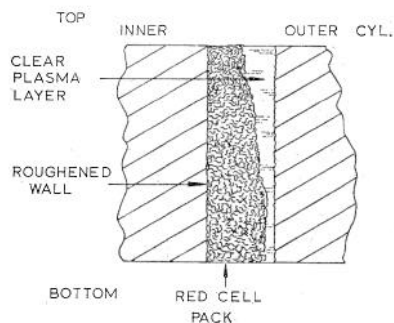


FIG. 2. Schematic diagram showing how clear plasma layer forms next to outer cylinder in coaxial cylinder viscometer.

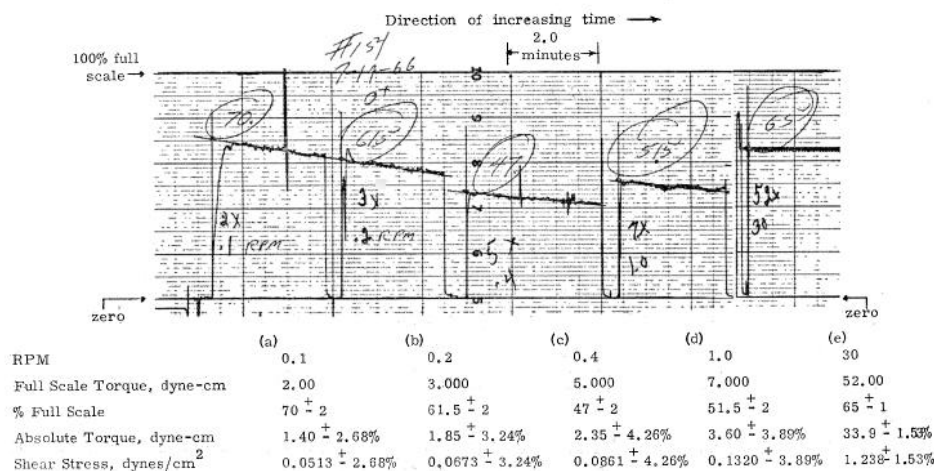


FIG. 3. Actual plot of torque as a function of time at constant rotational speeds—normal blood in coaxial cylinder viscometer.

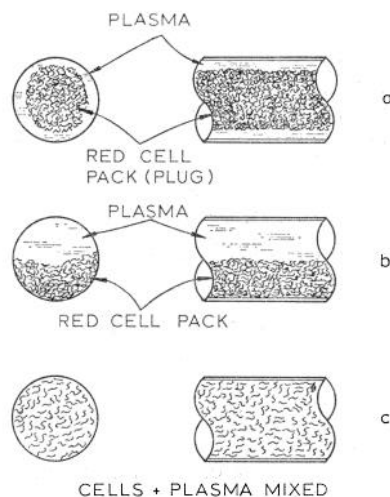
“rough” walls (grains of sand cemented to smooth surfaces, etc.) to mix the blood sample just prior to testing and to extrapolate the torque reading to zero time. Typical torque-time curves (32) are shown in Figure 3 for blood in a coaxial cylinder viscometer suddenly exposed to various steady values of strain rate (0.1, 0.2, 0.4, 1.0, and 30 sec^{-1}). The decreasing torque in the first four curves corresponds to the progressive formation of plasma-rich, red cell-poor layer (Fig. 2) next to a surface, even though the surface is roughened. The effect is much more severe if the surface is smooth. Figure 3 shows that by 30 sec^{-1} of strain rate,⁴ time dependence of the torque has disappeared, i.e., the blood stays “mixed.”

It is interesting to note that different investigators using identical Couette viscometers have come to contradictory conclusions about their experimental data; the origin of the contradiction lies principally in how the time-dependent variation of torque is interpreted.

In capillary viscometers operated under relatively high wall stresses (flow

⁴ The dimensions of this term are: $\text{cm} \cdot \text{sec}^{-1} \cdot \text{cm}^{-1}$; hence, sec^{-1} .

FIG. 4. Schematic diagram of blood in horizontal tubes (inner diameter 50–500 μ). *a*: Coherent plug of red cells, separated from wall by clear layer of plasma, moving slowly through tube. *b*: After a short period of rest (no flow), red cells settle to bottom section of tube and clear plasma occupies top section. *c*: After flow recommences, red cells become dispersed in plasma.



rates), blood remains sufficiently homogeneous to yield replicable measurement of its viscous properties provided that one does not attempt to operate the capillary as a falling meniscus viscometer (which entails the artifact of the rigid surface film). Even the best designed capillary viscometer is likely to yield nonreplicable data if blood is allowed to stand in the capillary for more than a few seconds and if then flow is gradually reestablished such that the reduced velocity⁵ $\bar{u}$ is less than about 1 sec^{-1} . These conditions, well documented by cinephotomicrography, (31) bring about a gross layer of plasma next to the wall surrounding a core of red cells that, mutually adhering, flow as a plug (Fig. 4*a*). It is easy to misinterpret this extreme case of two-phase flow as evidence that blood is a Newtonian and relatively low-viscosity fluid near and at zero rate of strain.

Another aspect of capillary viscometry of blood often overlooked is the effect of sedimentation rate. One knows from the standard vertical tube tests (e.g., Westergren, Wintrobe) that the sedimentation rate is of the order of a few millimeters per hour (49). For ease of visualization, assume 3.6 mm/hr = 3600 μ /hr = 1 μ /sec. If we now consider a horizontal hollow fiber of 120- μ inside diameter carrying blood and stop the flow, the above figure would suggest that within 1 min the red cell interface should have settled down to about the midplane of the fiber. This is found to be approximately the case (31). On restarting the flow of blood thus settled, a gross flow of plasma above the settled pack of red cells is first noted, followed sooner or later by remixing of cells (Fig. 4*b*, evolving to Fig. 4*c*). (If, however, the flow is less than a reduced velocity of 1 sec^{-1} , mixing will be indefinitely delayed.)

⁵ Reduced velocity:

$$\bar{u} = \frac{\bar{V}}{D} = \left[\frac{Q}{\frac{\pi}{4} \cdot D^3} \right] \cdot \frac{1}{D} \quad (13)$$

In summary, therefore, viscometry of blood plasma is usually attended by surface film effects that can lead to gross errors. When the artifacts are removed, plasma is found to be Newtonian. Rheological measurements of whole blood at high strain rates is relatively simple inasmuch as it behaves as a homogeneous and Newtonian liquid. At low rates of strain (1 sec^{-1} and less), sedimentation and formation of a clear plasma phase may easily nullify the intended measurement or produce entirely wrong results. For this reason, speed of execution of the experiment becomes important, with a well-mixed sample.

IV. RHEOLOGY OF NORMAL HUMAN BLOOD

A. Basic Data

A sample of normal human blood drawn into ACD solution shows a relationship of shear stress to shear strain rate of which Figure 5 is typical (hematocrit, 40; fibrinogen concentration, 260 mg %; temperature 37 C). It is apparent that the non-Newtonian region is near the origin, i.e., below about 100 sec^{-1} of shear strain rate, and that the method of plotting in Figure 5 leaves much to be desired. The data points near the origin are crowded in such a way that it is not easy to ascertain whether the data are trending to zero stress at zero shear strain rate.

Other methods of plotting have been suggested, but probably most satisfactory is the double square root plot, also called a Casson plot (4), as shown in Figure 6. The data are those of Figure 5, but now the non-Newtonian region is much more clearly displayed and is seen to consist of a region of transition from the Newtonian region above about 100 sec^{-1} into another linear region extending between zero and about 20 sec^{-1} of shear strain rate. However, the data extrapolate along this linear section not to zero stress but a finite stress, the yield shear stress τ_y , of theoretical and practical clinical importance.

The existence of the yield shear stress has been disputed but has been confirmed experimentally by direct measurement in both Couette (7) and in capillary viscometers (23). As noted in section III, its measurement is attended by experi-

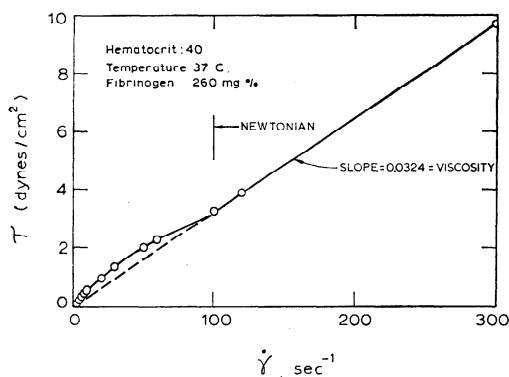


FIG. 5. Shear stress (τ) plotted vs. shear strain rate ($\dot{\gamma}$) for a typical normal blood (hematocrit 40; temperature 37 C). Note confusion of points near origin.

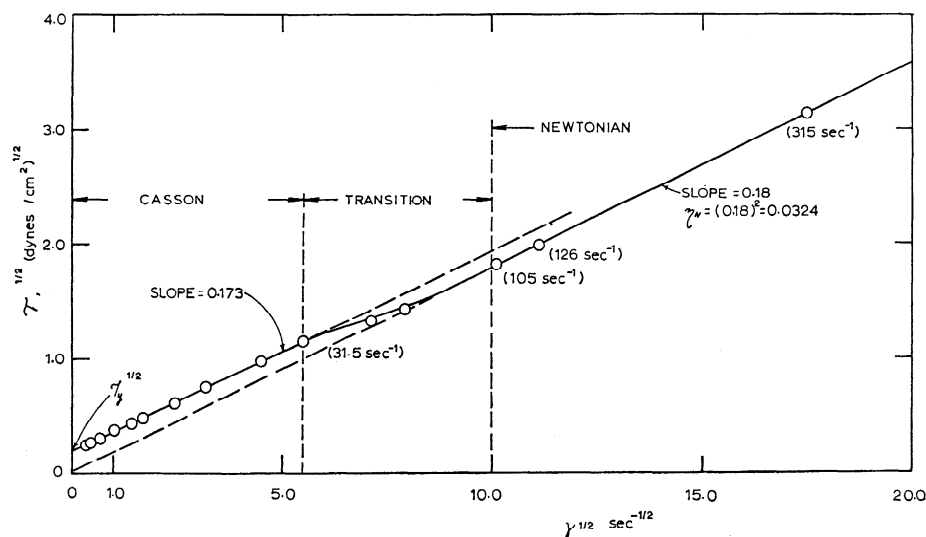


FIG. 6. Same data as in Fig. 5 replotted as square root of shear stress (τ) versus square root of shear strain rate ($\dot{\gamma}$) (hematocrit 40; temperature 37 C). Note determination of square root of yield stress $\tau_y^{1/2}$ by linear extrapolation.

mental difficulties, notable syneresis of plasma, formation of a plasma layer next to the boundary surface, and sedimentation, so that speed of measurement is essential. By proper execution, the yield shear stress as well as all other rheological properties can be replicated.

The curves for normal human blood, plotted as a Casson plot as in Figure 6, can be correlated (32) by two equations:

$$0-20 \text{ sec}^{-1}: \tau^{1/2} = \tau_y^{1/2} + \eta_N^{1/2} \dot{\gamma}^{1/2} \quad (14)$$

$$\text{above } 100 \text{ sec}^{-1}: \tau^{1/2} = \eta_N^{1/2} \dot{\gamma}^{1/2} \text{ or } \tau = \eta_N \dot{\gamma} \quad (15)$$

where τ = shear stress (dynes/cm²); τ_y = yield shear stress (dynes/cm²); η_N = ultimate Newtonian viscosity (poises, ca. 0.03–0.05); and, $\dot{\gamma}$ = shear strain rate.

Over the range of 20 to approximately 100 sec⁻¹ of shear strain rate, the shear stress-rate relationship is not easily expressed by any simple equation.

In numerous papers the rheological characteristics of blood have been expressed by the Casson equation written in the form:

$$\tau^{1/2} = b^{1/2} + s^{1/2} \dot{\gamma}^{1/2} \quad (16)$$

where s and b are in principle theoretically related to Casson's model. As demonstrated elsewhere (30) Casson's model is relevant only to very dilute suspensions of particles capable of forming rodlike aggregates. Its applicability to normal blood at hematocrit of about 40 seems untenable without drastic modification of some of the basic propositions. As a practical matter, one usually finds either that equation 14 is applicable, so that s of equation 16 is indeed η_N of equation 14, or that the data near zero shear rate on a Casson plot are so curved (see Fig. 8) that it is useless to attempt to force the linearization suggested by equation 16.

B. Hematocrit

It has long been recognized that the viscosity of blood increases with hematocrit.⁶ Data cited in most medical texts (i.e., 11) refer to high shear strain rate data, thus the range of applicability of *equation 15*, with the constant η_N of that equation ranging from about 0.03 poise at hematocrit of 40 to 0.10 at hematocrit 65. Furthermore, at least over the range of 0–50 hematocrit, the value of η_N in *equation 15* can be reasonably related to the hematocrit H by an equation attributable to Vand (42) for suspensions of rigid spheres, viz.

$$\eta_N = \eta_p \{1 + 0.025H + 7.35 \times 10^{-4}H^2\} \quad (17)$$

where η_p = plasma viscosity.

In the non-Newtonian regime, the effect of hematocrit is totally different. Over the range of hematocrit levels of 30–50 (determined by resuspending red cells in their plasma at different volume fractions) the yield shear stress is best correlated by an equation of the form:

$$\tau_y = A(H - H_c)^3 \quad (18)$$

where the limiting hematocrit H_c below which the yield stress is negligibly small is between 4 and 8 and the “constant” A (which in reality is a strong function of fibrinogen concentration) has a value of approximately $0.6\text{--}1.2 \times 10^{-6}$ for normal blood. The yield stress for blood hematocrit 40 is typically 0.04 dynes/cm².

C. Fibrinogen

The non-Newtonian rheology of blood is dominated by the interaction of fibrinogen (native, not activated, *not* fibrin) with red cells (9, 24, 26). At normal hematocrit levels, no other plasma protein in the absence of fibrinogen seems capable of producing a yield shear stress in red cells,⁷ although β -lipoprotein (29) has been implicated as having a synergistic effect with fibrinogen. The variation of the yield shear stress τ_y with fibrinogen concentration C_f at constant hematocrit probably is best correlated by the quadratic equation:

$$\tau_y = B C_f^2 \quad (19)$$

over the (normal) range of fibrinogen concentration of 100–400 mg %, as determined by isotonic⁸ dilution of various blood samples at constant hematocrit (24) and by analysis of a large number of samples (taken from blood bank donors), in which the endogenous fibrinogen concentration and measured yield stress were correlated, after adjustment of the hematocrit to a value of 40 ± 1 by centrifuga-

⁶ Several otherwise excellent studies on the basic fluid mechanics of suspended particles at low volume percent concentrations (38–40) seem misapplied to real blood, which in every sense is a concentrated suspension.

⁷ Packed red cells at hematocrit of 60 or greater, after washing in physiological saline, show significant yield shear stress.

⁸ Total osmolality constant, but diminishing colloid osmotic pressure.

tion and remixing. In *equation 19*, B varies between approximately 1.0×10^{-11} and 2.0×10^{-11} when C_f is expressed in milligram percent.

The "constant" B in *equation 19* is a weak function (24) of the concentration of all other plasma proteins except fibrinogen.

D. Temperature

In normal blood, at levels of shear rate such that *equation 15* is applicable, i.e., Newtonian flow, it has been shown that the temperature coefficient of viscosity is identical with that for water over the range of 10–37 C. Thus, in *equation 15* and again in *equation 17*, η_N and η_p vary with temperature exactly by the same percentage per degree as water (27).

In the non-Newtonian regime and at zero shear, the rheological properties of normal blood are less affected by temperature. The yield stress is found to be independent of temperature at least over the range of 37–15 C (27) for perhaps 90 % of the normal human subjects tested, but in the other 10 % there is a substantial increase of yield stress as temperature is decreased from 37 C to 25 C. The implication of this finding is deferred to the last section of this paper.

If the yield stress is not dependent on temperature, at least for the majority of human subjects, the activation energy for fibrinogen adsorption on red cells (the origin of the "structure" of blood) must be close to zero.

V. ABNORMAL HUMAN BLOOD

A. Polycythemia, Anemia

When the hematocrit exceeds 50 or thereabouts, blood shows various rheological abnormalities difficult to quantify. *Equations 17* and *18* do not necessarily apply, even crudely. The sedimentation rate, for example, usually goes to zero, even in the presence of fibrinogen, as a result of crowding of red cells. In fact, at hematocrit levels exceeding about 65, the dominant process underlying blood flow must be deformation of red cells. Any model suspension consisting of rigid biconcave discs of uniform size at a volume concentration of 65 % is either already a solid or a dilatant⁹ paste. Blood is therefore unusual in its ability to "flow" even at high red cell concentrations. A representative rheological diagram for polycythemic blood is given in Figure 7, the fibrinogen concentration being normal.

One notes a yield stress four times the normal value, which corresponds to A of *equation 18* equal to 1.1×10^{-6} (assuming H_c to be 4); and the ultimate Newtonian viscosity η_N is 0.066, corresponding to a relative viscosity of 7.7. *Equation 17* predicts a relative viscosity of 5.1. The agreement is reasonable in view of neglect of terms beyond the second power.

⁹ The viscosity rapidly goes to infinity as shear rate increases, like quicksand.

FIG. 7. Polycythemic blood (hematocrit 59.5) with normal fibrinogen concentration. Square root of shear stress (τ) vs. square root of shear strain rate ($\dot{\gamma}$).

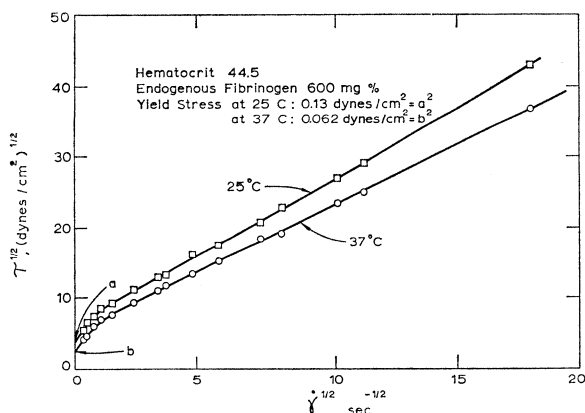
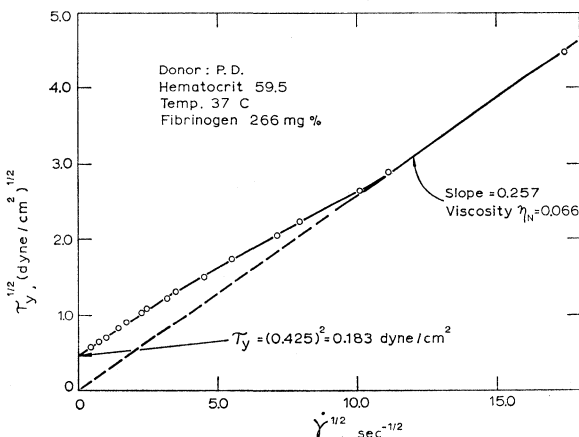


FIG. 8. Hyperfibrinogenemia, with nearly normal hematocrit. Square root of shear stress (τ) vs. square root of shear strain rate ($\dot{\gamma}$).

In general, anemic blood (hematocrit less than 30) displays nearly Newtonian behavior and the ultimate viscosity is reasonably well correlated by equation 17. Usually the yield stress is negligibly small. Only with hyperfibrinogenemia is there likely to be a significant departure from Newtonian flow.

B. Afibrinogenemia, Hyperfibrinogenemia

The rarely noted blood abnormality afibrinogenemia has been studied rheologically (24) with the finding that the sample having a normal hematocrit showed substantially no yield stress and an almost constant viscosity. This result is in accord with experiments on suspensions of red cells in saline and in serum (25).

Hyperfibrinogenemia produces elevations in yield stress (cf. eq. 19) and, as is well known, a high sedimentation rate at usual levels of hematocrit. The high sedimentation rate complicates rheological determinations, for reasons given in section III. One example of hyperfibrinogenemic blood (600 mg% fibrinogen) having an approximately normal hematocrit is represented in Figure 8 (E. W.

Merrill and R. Replogle, unpublished data). The relationship between shear stress and shear strain rate is markedly curved below an abscissa value of $2.5 \text{ sec}^{-1/2}$. (Thus, *eq. 14* is not obeyed). The Newtonian relation given by *equation 15* is not attained at a value of shear strain rate of 300 sec^{-1} (abscissa value 17.7), although presumably it would be found at a higher value of shear strain rate. Further, there is a twofold difference in the extrapolated values of yield stress at 25 C and at 37 C (in contrast to normal blood, *sect. ivD* above).

An especially important clinical case, tetralogy of Fallot, frequently produces concomitant polycythemia and hyperfibrinogenemia (37). As is evident from the appearance of the patient, peripheral circulation is drastically impaired. The rheological characteristics of the blood—describable as a paste—are extraordinarily high levels of yield shear stress and of the ultimate viscosity, η_N .

C. Diabetes Mellitus

Merrill (unpublished results) in collaboration with the Joslin Center (Boston) concluded that blood from patients with diabetes mellitus in various stages shows no rheological characteristics truly different from nondiabetic human blood of equal hematocrit and fibrinogen concentration. Blood sugar levels per se have been demonstrated to have no effect whatever on rheology (5).

D. Hyperlipemias

Despite an early publication (28) suggesting that high levels of triglycerides in plasma produce a substantial negative temperature coefficient of yield stress (low temperature: high yield stress), it has been impossible to substantiate this by other experiments. It seems likely that, in most cases of hyperlipemia, the rheological properties of blood are not significantly different from those of normal blood and that, when the negative temperature coefficient of yield stress is noted, it signifies some special micellar organization of the lipid and, most probably, a specific interaction of lipids and protein or lipids and lipoproteins (29).

E. Plasma Protein Abnormalities Other Than Fibrinogen

1) *Lipoproteins*. It is extremely difficult to gain clear-cut evidence on the effect of lipoproteins. One report (29) on artificial suspensions of red cells in various protein fractions suggests that β -lipoprotein has a significant synergistic effect in enhancing yield stress, but only in the presence of fibrinogen and cannot produce a yield stress in the absence of fibrinogen.

2) *Hyperproteinemia*. A weak trend toward increase of yield stress (at constant hematocrit and fibrinogen concentration) with increase in total plasma protein concentration is reported (24), based on normal blood donor samples over the range of concentrations 5.2–6.4 g %. The origin of this effect may lie in the displacing of equilibrium between fibrinogen adsorbed on the red cell surface and

free fibrinogen in solution. It is not clear whether these data can be reasonably extrapolated to hyperproteinemia.

3) *Cryoglobulinemia*. As expected, cryoglobulinemia leads to drastic increase of yield stress as temperature is decreased below 37 C even a few degrees. Precipitation of the globulins confuses the experimental measurement. There can be no doubt of the profoundly deleterious nature of this temperature response from the viewpoint of flow in the microcirculatory vessels (12).

4) *Macroglobulinemia*. Wells (47) reports significant increase of yield stress and non-Newtonian behavior in the low-shear regimen of samples drawn from patients suffering from macroglobulinemia, as compared with controls at equal hematocrit and fibrinogen level. One can postulate, while awaiting further experimental evidences, that: a) the macroglobulins are directly adsorbed on the red cell surface and are capable of sticking two surfaces together via some sort of bridge, like fibrinogen; or b) the macroglobulins bind to fibrinogen already adsorbed on the surface and enhance the bridging already possible with fibrinogen.

F. Blood After Extracorporeal Circulation

In this type of circulation (17), including heart-lung machines, such a wide range of rheological abnormality has been reported that it is difficult to offer a useful generalization. There are at least three common factors to consider: 1) free hemoglobin in the plasma, 2) erythrocyte ghosts, and 3) fragments of denatured plasma protein/lipid films resulting from direct contact with air or oxygen.

The rheological effect of free hemoglobin, within clinically relevant limits, is not impressive. There is a small trend toward increase of the yield stress with increasing free hemoglobin concentration (6).

The rheological properties of suspensions of lysed red cells (ghosts) prepared by osmotic lysis as compared with intact cells suggest that fibrinogen continues to be effective in forming (under stasis) network aggregates of ghosts, as in the case with whole blood. There is no evidence to suggest that in actual mixtures containing mostly intact red cells and a small percentage of ghosts, as produced in the extracorporeal circulation, there is a significant rheological change on this account.

By far the most important rheological alteration is produced by the denatured protein-lipid film, probably acting on the red cell membrane. Several effects are well known: that the rate of hemolysis is rapidly increased by an fluid mechanical pattern in the presence of air bubbles (46) as compared with the identical pattern without bubbles; that in disc oxygenators a sludge is produced that by analysis is found to contain high concentrations of proteins and lipids; and that the blood usually has an abnormally high sedimentation rate. All these factors point to aggregation of red cells by the denatured material, over and above the effect (reversible) of fibrinogen.

Direct rheological tests on blood oxygenated by direct contact with air (as in a heart-lung machine) usually show: 1) elevated yield stress; 2) poor replicabil-

ity, probably the result of sedimentation; and 3) poor correlation by the linearization of the Casson equation (6).

VI. EFFECT OF ADDITIVES ON BLOOD RHEOLOGY

A. Anticoagulants

It is extremely difficult to devise an *in vitro* test for the rheological properties of blood without the use of an anticoagulant and thus to make a comparison between the properties of blood in the circulation and after addition of anticoagulants.

Cokelet (6) studies in a Couette viscometer blood freshly drawn from a donor next to the instrument (before clotting occurred) and, after making allowance for dilution of plasma proteins when an aqueous solution of anticoagulant was used, concluded that none of the following anticoagulants used in any reasonable concentrations produced any significant change of the rheological properties compared with the control: heparin, sodium citrate, ACD, EDTA (ethylenediaminetetraacetate-sodium salt), sodium oxalate.

From these observations it is concluded that the level of free ionic calcium in the plasma, which would be drastically diminished by all of the listed anticoagulants except heparin, does not play a role of any observable significance in the fibrinogen-red cell structure.

B. Saline Solution

In the limited circumstances in which it might be feasible to dilute whole blood with isotonic saline solution, the only effect is to reduce the yield stress by diminution of hematocrit, more or less following *equation 18* and concomitantly, by diminution of fibrinogen concentration, *equation 19*, whereas the ultimate Newtonian viscosity is reduced approximately according to *equation 17*. In brief, the blood in all respects becomes "thinner" in a predictable way. The rheological effects of significant change of *total* osmotic pressure by the addition to blood of hypertonic or hypotonic saline solutions have been reported by Meiselman et al. (20). In general, the changes in rheological characteristics with change in total osmotic pressure are negligible in the range compatible with life, namely 303 ± 5 milliosmoles/liter. The yield stress at a constant volume fraction of packed cells (hematocrit) is slightly increased as the plasma becomes hypotonic (< 303 milliosmoles/liter), perhaps because a loss of biconcavity in the red cell as it expands thus permits a greater contact between the cell faces and thus a more effective bridging of cells by fibrinogen.

C. Plasma Expanders, Substitute Plasma

As is well known, simple saline solutions are of little clinical value because they lack the colloid osmotic pressures whereby they may be retained in the circu-

TABLE 1. *Ideal colloid osmotic pressure and relative viscosity (η_{rel}) produced by albumin in saline compared with dextran types, at equal concentrations of 3.0 g/dl*

Macromolecule	$\bar{M}_n$	$\bar{M}_w$	$[\eta]$,* dl/g	π° , atm	η_{rel} (25 C)
Albumin	67,000	67,000		0.0113	1.1
Dextran					
40	26,000*	40,000*	0.20*	0.029	1.726
80	48,000*	75,000*	0.26*	0.0157	2.00
110	80,000*	114,000*	0.32*	0.0094	2.28

$\bar{M}_n$ = number-avg mol wt. $\bar{M}_w$ = wt-avg mol wt. $[\eta]$ = intrinsic viscosity. $\pi^\circ = \frac{CRT}{\bar{M}_n}$; second and higher virial terms neglected ($T = 37^\circ\text{C}$, $C = 0.03\text{ g/ml}$). η_{rel} = solution viscosity/solvent viscosity: solvent = isotonic saline; $\eta_{rel} = 1 + [\eta]C + k'[\eta]^2C^2$ (C = concn., g/dl, $k' = 0.35$). * Data as reported by manufacturer (Pharmacia).

lation. Among the clinical alternatives are albumin solutions or other plasma protein preparations free of fibrinogen and saline solutions of miscellaneous random-coiling macromolecules, whether of biological or synthetic origin.

Colloid osmotic pressure is dictated by *number-average* molecular weight whereas solution viscosity is governed in a complicated manner by *weight-average* molecular weight plus a host of other considerations; the net result is that saline solutions of the plasma proteins at a given level of concentration and of molecular weight *always* show a considerably lower viscosity than solutions of random-coiling macromolecules. Table 1 compares the relative viscosity of albumin in saline to the relative viscosity of dextrans at equal concentration (3 g/dl), (dextrans representing random-coiling macromolecules), as well as the "ideal" colloid osmotic pressure (neglecting second-order and higher terms in the virial expansion¹⁰).

1) *Albumin solutions*. To decrease blood viscosity in vivo by dilution, albumin solutions at a concentration of 3–3.5 g % in isotonic saline are more effective per volume added than any other known fluid. The generalizations concerning saline solutions are applicable directly: no known rheological complication ensues when albumin is added to red cell suspensions. The considerations against the use of albumin are those of cost of preparation, fractionation, storage, etc.

2) *Dextrans*. Dextrans, all factors considered, are probably next best after albumin solutions. It is true that, at equal hematocrit and fibrinogen concentra-

¹⁰ The complete equation is:

$$\frac{\pi}{CRT} = A_1 + A_2C + A_3C^2 + \dots$$

where the "ideal" term is $A_1 = 1/M$, succeeding terms involving A_2 , A_3 , etc., being neglected. C is the colloid concentration in g/cm³; M , its molecular weight; R , gas law constant; T , absolute temperature; and π , osmotic pressure. "Colloid" implies a molecular species sufficiently large to be incapable of diffusing through the membrane of an osmometer.

tions, the dextrans exceeding 40,000 wt-avg mol wt increase the yield stress compared with the control, and indeed experimental types exceeding 120,000 mol wt powerfully flocculate red cells (21).

Per unit concentration in blood, dextran of lowest molecular weight affords both the highest colloid osmotic pressure and the least tendency either to increase plasma viscosity or, more importantly, red cell adhesion. On the other hand, if the number-average molecular weight is much less than 60,000 (compared with albumin at 67,000) the dextran will be rapidly excreted through the kidney. Thus, narrow practical limits are placed on the molecular weight of the dextran employed clinically.

VII. MAMMALIAN BLOOD OTHER THAN HUMAN

Dog blood (37) has been investigated in the low-shear regime (less than 100 sec^{-1} shear rate) over which human blood displays its non-Newtonian properties with substantially the same findings, viz., that the non-Newtonian properties are the same in kind, and virtually in degree, and reflect the reversible structuring ascribable to the interaction of fibrinogen with red cells. In dog blood the median fibrinogen concentration is higher and consequently the median yield stress is higher than in human blood.

It is difficult to perform accurate rheological studies on the blood of rodents because of the small volumes of blood that may be withdrawn without sacrificing the animals. The blood of the golden hamster may be representative of rodent blood. Its rheological properties were studied by Berman et al. (1) and were found to be qualitatively similar to other mammalian blood: yield stress varies with fibrinogen concentration and with hematocrit; at normal levels of either in the hamster, the yield stress is around 0.02–0.04 dynes/cm².

Hamster blood has been particularly interesting to study rheologically because one can, in the cheek pouch, study flow patterns¹¹ in the microcirculation by cine-photomicrography (1, 2, 10) and correlate qualitatively the flows observed with the rheological characteristics measured; the unequivocal result is that as yield stress increases for whatever reason, venular flow appears slower and stasis is more frequent.

The rheological properties of blood of the rhesus monkey and the baboon have been studied by Merrill (unpublished results). In no respect are these properties significantly different from human blood, as expressed by *equations 14, 15, 18, and 19*.

¹¹ It is surprising that in the literature so much emphasis has been placed on annular layers of clear plasma at the wall of the living vessel in spite of the cinematographic proof that under normal conditions no such layer exists. When a layer exists it is usually as a consequence of stasis, a thrombus, a pavement of leukocytes, or some other exceptional circumstance—and in these cases the complications of the two phases (plasma, packed cells) and the vessel geometry make fluid mechanical analysis virtually impossible. Plasma skimming, a process well documented by cinephotomicrography (10), is not to be confused with the hypothesized coaxial annular plasma slip layer.

VIII. INDIRECT RHEOLOGICAL TESTS OR SIMPLIFIED TESTING

A laboratory procedure whereby the rheological characteristics of blood could be simply assessed on a very small blood sample with inexpensive equipment would be of considerable practical utility.

No single test is really satisfactory. The sedimentation-rate tests (49) are found to reflect crudely the fibrinogen concentration, if proper cognizance is taken of hematocrit. As is well known, a sample can be sufficiently polycythemic so as not to settle at all.

The sedimentation-rate test is disappointing in its nonreproducibility, especially on aged blood. Since an "induction period"¹² is almost invariably found, which is of variable duration, the usual reading of red cell bed level at the end of 1 hr is of little value (33).

Perhaps the best rheological test that can be performed with simple inexpensive equipment on blood samples that are neither polycythemic nor hyperfibrinogenemic is by means of the Wells-Brookfield cone-on-plate viscometer (48) in which the measurements are made at two speeds corresponding to 10 and 100 sec^{-1} of shear strain rate. Following the method of plotting on double square root coordinates that leads to *equations 14 and 15*, the high-speed point (100 sec^{-1}) locates the upper Newtonian viscosity η_N (32). The low-speed point (10 sec^{-1}) lies on a line parallel with one drawn from the origin through the coordinates of the high-speed point. Thus, extrapolation to zero shear strain rate leads to an approximate value of the square root of the yield shear stress. At these two speeds the sample remains sufficiently mixed to avoid the artifacts mentioned earlier that arise from a clear plasma layer next to the cone.

IX. PHYSIOLOGICAL SIGNIFICANCE OF BLOOD RHEOLOGY

Having surveyed the unusual rheological characteristics of blood that manifest themselves at low rates of shear, we must finally inquire about their relevance to physiology.

It is difficult, on the one hand, to cite any one example where the data can be used as the basis of an exact quantitative calculation of the flow-pressure relation, and it is impossible, on the other hand, to dismiss these characteristics as irrelevant to flow in the living circulation, except in one site: the capillary.

Although gross rheological properties reflect red cell-to-red cell interactions,

¹² During the induction period in normal blood, red cells are forming rouleaux, which in turn associate into larger aggregates and superstructures extending to and adhering to the walls of the containing tube, while plasma is being segregated into the spaces between the red cell network. At a certain time, around 5–15 min, the total weight of the red cell network exceeds the capacity of red cells adherent to the wall to hold the column and the column starts to collapse (beginning of "sedimentation"), accompanied by upward flow of plasma through the downward movement of the red cells. Thus, the yield stress of blood and the induction time of blood are related in a complicated way.

they reveal nothing about specific red cell-to-capillary wall interactions and little about the deformability of the red cells at normal levels of hematocrit. As shown by Weed et al. (45), at hematocrit levels of around 80, stiffening of red cells produces a great increase in viscosity and yield stress, even when the red cells are suspended in physiological saline.

Passing through large vessels, red cells are randomly subjected to deforming forces by collisions with their neighbors during time intervals of the order of milliseconds, and they act "springy." Forcing red cells individually through micropipettes or filters may involve much longer time intervals of net stress, causing the red cell membrane to exhibit "creep," as if by a viscoelastic process. Study of the deformability of the red cell (microrheology of a single cell) from the biconcave disc shape by these experiments (35, 36, 41, 45) is in itself a fascinating and fertile area of research. Presumably the spleen makes its separation of red cells according to whether they can deform sufficiently to pass the capillaries, the lumen of which is far smaller than the diameter of the unperturbed cell.

Blood rheology appears most relevant to "slow flows," flows in which the blood can be treated as a continuum and in which the mean shear stress (proportional to pressure gradient times lumen diameter) is relatively low. This means flow in venules "most of the time" and flow in certain veins (leg of standing man) "some of the time." Those who have studied venular flows in animal preparations note the stop-start nature of these flows. What we have to add here is that, to recommence the flow after it has stopped, a finite pressure is required to overcome the yield stress (disperse red cells from their aggregated state). This pressure must increase approximately as the third power of the hematocrit and the square of the fibrinogen concentration.

Blood rheology *might* be viewed as irrelevant to arterial and arteriolar flows on the grounds that in general the flow velocity is sufficiently high that mean shear stress in the vessels corresponds to the Newtonian part of the total shear stress-shear strain rate function (Fig. 6). Such a view is not justified without better experimental evidence than now exists for the following reasons. As is well known, dilute polymer solutions found to be completely Newtonian by viscometry interact strongly in flow situations where there are rapid rates of change of shear stress, as in turbulence, around an obstruction, at a branching division of a conduit, etc. (44). The direction of the interaction is to reduce the pressure driving force and reduce the degree of mixing as compared to a pure solvent of the same viscosity. The same effects, less pronounced, have been found in Newtonian suspensions of solid microspheres (13). Now, if in addition there is a specific red cell-to-red cell interaction (via fibrinogen), the effects of nonmixing are likely to be magnified, especially when, as after a branching junction of an artery, there is a region of flow separation. This may also occur in the large arteries when a back flow occurs at the axis with a forward flow nearer to the wall during that part of the cardiac cycle just before systole, as a result of the phase relationship between elastic deformation of the arterial wall and the pressure wave. Thus one might anticipate rather significant differences of flow patterns in the arterial circuit with blood as compared to

Newtonian liquids (e.g., glycol-water) of equal Newtonian viscosity, and this is an area needing further study. Unfortunately, conventional methodology utilizing the Pitot tube and hot-film anemometry (44) seems useless because of the impingement of red cells on the probe and the consequent drastic alteration of the local flow pattern—in other words, the consequent impossibility of a meaningful calibration of the probe.

At the end of the arterial-arteriolar tree (precapillary sphincter) blood rheology may have considerable significance, in the following way. Though the cross section of the vessel just before the sphincter is only a few red cell diameters—thus too small to permit strict application of the properties of blood as a continuum—nonetheless it is in this sharply converging section where red cell-red cell sticking would be particularly important. One can visualize this qualitatively by thinking of what would happen if the grains of sand moving down into the throat of an hourglass (3-min egg timer) were slightly sticky toward each other. After a particular precapillary sphincter has closed off a flow, the restarting of the flow necessitates the disintegration of a temporary red cell network, the cohesiveness of which is proportional to the yield stress.

In summary, the relevance of blood rheology to physiological fluid mechanics is to make stopping of flows easier, starting of flows more difficult, and slow flows more energy consuming than would be expected if blood were a simple, cell-less, micromolecular fluid of equal viscosity—and these effects are increasingly emphasized with increase of hematocrit and fibrinogen concentration. Direct experimental correlation between *in vivo* circulation and blood rheology (37) supports this interpretation. Equally important is the implication of rheological properties with platelet thrombosis and fibrin thrombosis. The effect of a thrombus is to retard or stop a flow. The blood thus stopped or retarded should “protect” the thrombus, because either through its yield stress, if stopped, or through high viscosity it should support part of the pressure drop that is operating to dislodge the thrombus. Concomitantly, the growth of a thrombus through any enzymatic sequence including the amplifying “waterfall sequence” of the intrinsic system (8, 19) would be favored kinetically because of resistance of the immediately adjacent blood to mixing, therefore to dilution of activated enzymes (or platelets). Put another way, the rheological properties of blood would be such as to favor maintaining concentration levels of activated clotting factors critical to the next enzymatic step and finally to the process of fibrinogen polymerization into fibrin. This final step (fibrinogen → fibrin) is particularly interesting because static blood presumably has fibrinogen organized (24) in a special way on the contiguous red cell surfaces. Thus, in the growing fibrin thrombus, the red cells should be particularly favored for incorporation, and the structural integrity of the thrombus should be improved by the incorporation of red cells as fix points in the fibrin network like a reinforcing filler in rubber technology. The correlation of thrombus-induced stroke with hematocrit level in the Framingham, Massachusetts, study by the U. S. Public Health Service in 1967 (15) suggests that a worthwhile sequel study would be correlation with hematocrit *and* endogenous fibrinogen concentration, thus with

precisely those two factors that principally govern the rheological properties of blood.

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