Effects of hematocrit and plasma proteins on human blood rheology at low shear rates[1]

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CHIEN, SHU, SHUNICHI USAMI, HARRY M. TAYLOR, JOHN L. LUNDBERG, AND MAGNUS I. GREGERSEN. *Effects of hematocrit and plasma proteins on human blood rheology at low shear rates.* J. Appl. Physiol. 21(1): 81–87. 1966.—The viscosity of whole blood, defibrinated blood, and Ringer suspension of cells was determined at shear rates from 52 to 0.01 sec^{-1}. At each shear rate, the viscosity of each system rises as the hematocrit (H) is increased from 0 to 95%. Plasma, serum, and Ringer solution exhibit Newtonian behavior. At 45% H, shear-rate dependence of viscosity is greatest in whole blood and almost absent in Ringer suspensions. The Ringer suspensions depart progressively from Newtonian behavior with increasing H. At 90% H, the viscosity values as well as their shear-rate dependence are nearly equal in all three systems. In whole blood, square root of shear stress does not show a linear relation to the square root of shear rate. Data on shear rates down to 0.01 sec^{-1} indicate that whole blood possesses no yield stress. In whole blood with normal H, non-Newtonian behavior results primarily from cell-protein interactions. As H is raised toward 90%, contributions by direct cell-cell interactions become increasingly more important.

fibrinogen; Newtonian flow; shear stress; viscosity; yield stress

THE VISCOSITY of blood depends on the shear rate. Following the introduction of low shear-rate viscometers (6, 8) it has been shown that blood viscosity increases markedly as the shear rate approaches zero. The shear rates in the circulatory system vary both spatially and temporally and are difficult to determine. Measurements of flow velocity in postcapillary venules (21) indicate that the shear rate in this region is rather low. Furthermore, blood flow in the cheek pouch of healthy hamsters ceases intermittently (7), indicating that conditions near or at zero shear rate exist normally in the microcirculation. In various forms of circulatory shock, flow rates near or at zero undoubtedly exist.

Recent experiments by Merrill, Wells, and their colleagues have studied several factors that influence blood viscosity at low shear rates. For example, the influence of the suspending medium was investigated by removing all plasma proteins (23), removing fibrinogen (14), or adding fibrinogen (22). In these experiments, the hematocrit was kept constant in a normal range. Experiments were also performed by Merrill et al. (16) to study the effects of varying the hematocrit (from approximately 6 to 60%) on the viscosity of whole blood. In our laboratories, the effects of the hematocrit level on blood viscosity has also been investigated (9–11), but the results on low shear rates were not reliable because of the instrumental limitations of our original G.D.M. (8) viscometer. Since then, the mechanical as well as the electronic components of the viscometer have been improved and measurements at shear rates as low as 0.052 sec^{-1} and finally to 0.01 sec^{-1} have become reproducible. This permitted us to reinvestigate systematically the effects of hematocrit and plasma protein concentration on blood viscosity at low shear rates. Three types of samples were used: heparinized whole blood, defibrinated blood, and Ringer suspension of cells. In each type of preparation, hematocrit was varied from 0 to approximately 95%. Therefore the materials used in the present experiments differ from those in the literature in that *a*) a wider range of hematocrit was studied on whole blood, including blood samples consisting of almost purely packed cells, and that *b*) studies on the effect of hematocrit on viscosity were extended to include samples in which fibrinogen or all plasma proteins had been removed. It was hoped that such a study of the combination of the hematocrit factor and the plasma protein factor would enable the separation of the roles of the cell-protein interactions and cell-cell

Received for publication 23 March 1965.
[1] The work reported here was done under Contract DA-49-193-MD-2272 between the US Army Medical Research and Development Command and Columbia University. This investigation was also supported by National Heart Institute Research Grant HE-06139 and by several private donors including the Mary Evelyn Townsend Fund, the Brook Foundation, Mrs. George W. Perkins, and Mrs. Alan M. Scaife.

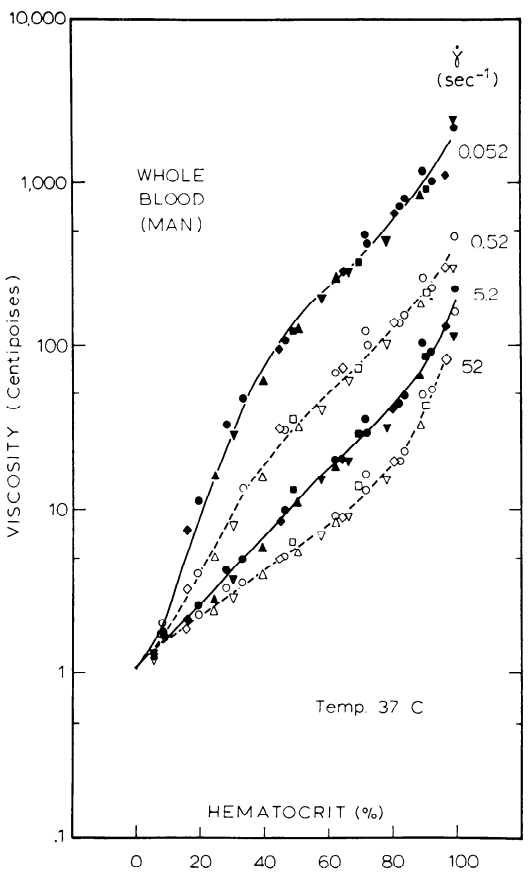

FIG. 1. Relationship between the logarithm of viscosity at four different shear rates and the hematocrit of whole blood. Closed symbols represent the data at shear rates of 0.052 and 5.2 sec^{-1} and open symbols depict the results at shear rates of 0.52 and 52 sec^{-1}. Symbols of different shapes are used to indicate results on each of five subjects. The lines drawn to fit the data are described by *equation 1* with the constants listed in Table 1.

interactions[2] in contributing to the non-Newtonian behavior of blood, thus shedding some light on the rheology of blood at low shear rates.

METHODS

Blood Samples. Whole blood was drawn from the antecubital vein of healthy human subjects into evacuated tubes containing heparin (Becton and Dickinson, Rutherford, N. J.). For the preparation of protein-free cell suspensions, heparinized whole blood was centrifuged and plasma removed. The cells were then washed three times with a Ringer-Locke solution (NaCl 0.9 g/100 ml, KCl 0.42 g/100 ml, $CaCl_2$ 0.42 g/100 ml, $NaHCO_3$ 0.02 g/100 ml) by mixing and centrifuging. For the preparation of defibrinated blood, blood was drawn into containers without heparin and a copper-wire network was rotated gently in the blood sample until some 5 min after the fibrin clot had formed. Blood defibrinated in this manner did not show any alteration in cell percentage or serum protein concentration, but contained no fibrinogen.

For each type of preparation (whole blood, defibrinated blood, and Ringer suspension of cells), series of samples were prepared with various hematocrit levels (from 0 to approximately 95%) by increasing or reducing the volume of the suspending medium. The hematocrit was determined after spinning in a microcentrifuge (Clay-Adams, N.Y.) for 5 min at 15,000 × *g*. Under these conditions there was only a negligible amount of plasma (average 1%) trapped in the packed cell column (3) and the plasma trapping factor (4) was therefore ignored.

Viscometry. A modified version of the G.D.M. viscometer was used. The operational principle of the G.D.M. viscometer has been described elsewhere (8, 15). The viscometer consists of coaxial cylinders separated by a small annulus (0.960 mm) in which the sample is located. The inner cylinder (or rotor) can be raised or lowered into the outer cylinder and is driven by a motor system to rotate at any speed varying from less than 0.01 to over 50 rev/min. The motor is powered and controlled by tachometer and feedback amplifier systems (Servo-Tek Corp. Hawthorne, N.J.), such that a high degree of precision is attained throughout the range of rotation used in the present experiments.[3] The outer cylinder (or the sampling cup) rides on a nitrogen gas bearing. The latter contains torque-sensing elements connected through feedback amplifiers (Dynamics Research Corp., Stoneham, Mass.) to an electromagnetic torque-generator which generates torque to maintain the constancy of the position of the bearing and the cup. Therefore, when the rotor is rotated at a given rate, the torque produced in the sample is balanced by the magnetic countertorque, which is recorded. The torque (dynes-cm) is directly proportional to the shear stress (τ, dynes/cm^2) at the inner surface of the outer cylinder and the proportional factor was determined with the use of standard oils (National Bureau of Standards, Washington, D.C.). The geometry of the viscometer is such that the shear rate ($\dot{\gamma}$, sec^{-1}) is equal to 1.04 times the rate of the rotor rotation (rev/min). Viscosity (η, centipoises) was calculated as $100\ \tau/\dot{\gamma}$. The rotor and the cup are smooth and not grooved. A guard ring is present between the two cylinders and projected below the sample surface to minimize surface film forces.

All viscosity measurements were made at 37 C. This temperature is maintained in the system by forcing water from a water bath through a channel inside of the rotor. At the exit from this channel, a thermistor is inserted and it is connected to a thermoregulator (Thermonitor, E. H. Sargeant & Co., Springfield, New Jersey) and a heater in the water bath. Determinations

[2] The term "cell-cell interactions" is used to denote the direct interactions among cells independent of the presence of proteins; e.g., the crowding and deformation of cells at high cell concentrations. In contrast, the term "cell-protein interactions" refers to the interactions of cells with plasma proteins, including cell-protein-cell interactions. Thus the formation of rouleau or other cell aggregates in the presence of proteins is a form of cell-protein interaction.

[3] The authors thank Walter Logan of the Bell Telephone Laboratories, Inc., for his major contributions to the design of the drive system.

TABLE 1. *Constants for equation 1 relating viscosity to hematocrit*

Type of Sample	Shear rate, sec^{-1}	a_0, $\times 10^{-1}$	a_1, $\times 10^{-2}$	a_2, $\times 10^{-3}$	a_3, $\times 10^{-5}$	a_4, $\times 10^{-7}$	a_5, $\times 10^{-9}$
Whole blood	52	2.028	2.928	−0.157	1.385	−2.813	1.788
	5.2	1.817	2.423	0.985	−1.372	0.299	0.353
	0.52	1.499	2.599	3.598	−9.467	9.524	−3.335
	0.052	1.342	4.250	5.820	−16.425	16.958	−6.035
Defibrinated blood	52	1.336	5.467	−1.669	4.439	−5.242	2.381
	5.2	0.813	4.245	−0.430	2.456	−4.051	2.097
	0.52	1.260	4.130	−0.093	3.228	−6.098	3.147
	0.052	0.681	−0.344	4.383	−7.353	4.446	−0.700
Ringer suspensions of cells	52	−3.651	4.131	−0.970	4.060	−6.172	3.186
	5.2	−3.644	2.160	0.314	1.763	−4.134	2.397
	0.52	−3.658	4.237	−1.508	6.796	−8.961	3.908
	0.052	−3.760	3.763	−0.645	3.802	−4.073	1.369

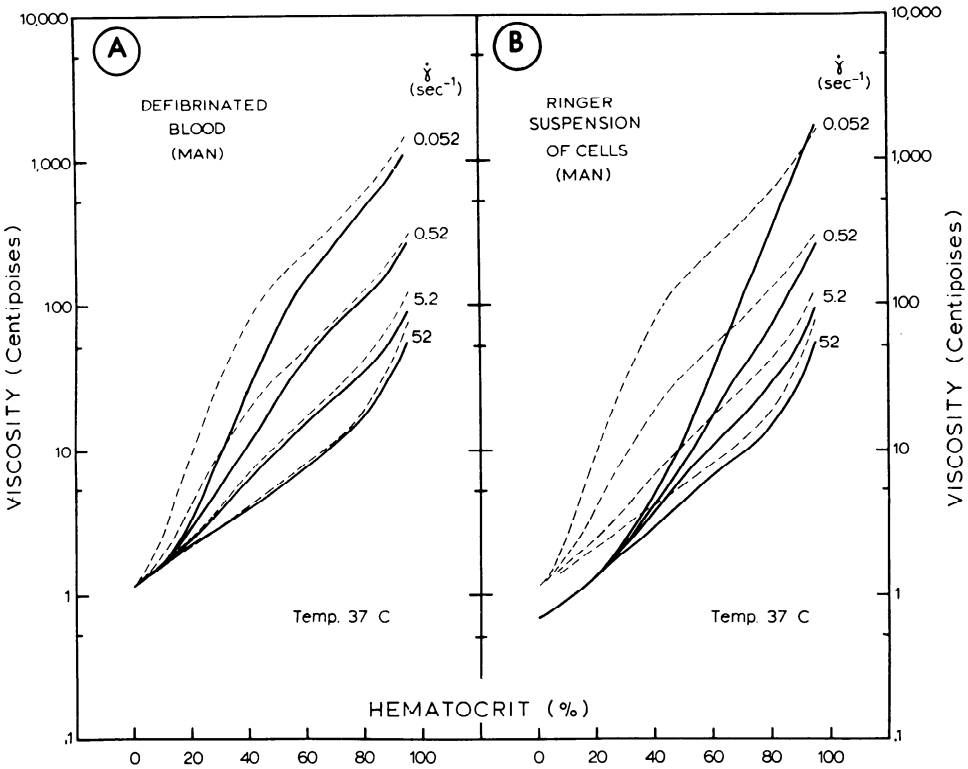

FIG. 2. Relationship between the logarithm of viscosity at four shear rates and the hematocrit in defibrinated blood (*A*, solid lines) and Ringer suspensions of cells (*B*, solid lines). The dotted lines in *A* and *B* represent the results on whole blood (from Fig. 1). The lines are described by *equation 1* with the constants listed in Table 1.

of sample temperature showed that it was maintained within ±0.1 C.

RESULTS AND DISCUSSION

The results on the viscosity of whole blood at four shear rates (52, 5.2, 0.52, and 0.052 sec^{-1}) are shown in Fig. 1, where the logarithm of viscosity is plotted against the hematodrit (H). The viscosity of plasma (H = 0) is independent of shear rate, and hence plasma is a Newtonian fluid. The viscosity of whole blood is shear-rate dependent. At each shear rate, the viscosity increases progressively with rising H. For whole blood (Fig. 1), defibrinated blood (Fig. 2*A*) and Ringer suspensions of cells (Fig. 2*B*), the complex curvilinear relations between the logarithm of viscosity and H are represented empirically by fifth power polynomials, which are found to describe the data more faithfully than lower power fittings.

$$\ln \eta = a_0 + a_1 H + a_2 H^2 + a_3 H^3 + a_4 H^4 + a_5 H^5 \qquad (1)$$

The constants (a_0 to a_5), determined by least-square fitting of the data in a computer (IBM 7094), are given in Table 1. Although non-Newtonian behavior is found in whole blood with H less than 10%, it is not seen in defibrinated blood at H below 15% (Fig. 2*A*) or in Ringer suspensions of cells at H below 30% (Fig. 2*B*). Therefore at low H, the non-Newtonian behavior of whole blood is primarily due to the presence of fibrinogen and also partially due to the presence of other proteins. The differences in viscosities between whole blood and Ringer suspensions of cells or defibrinated blood cannot be explained on the basis of the differences in the vis-

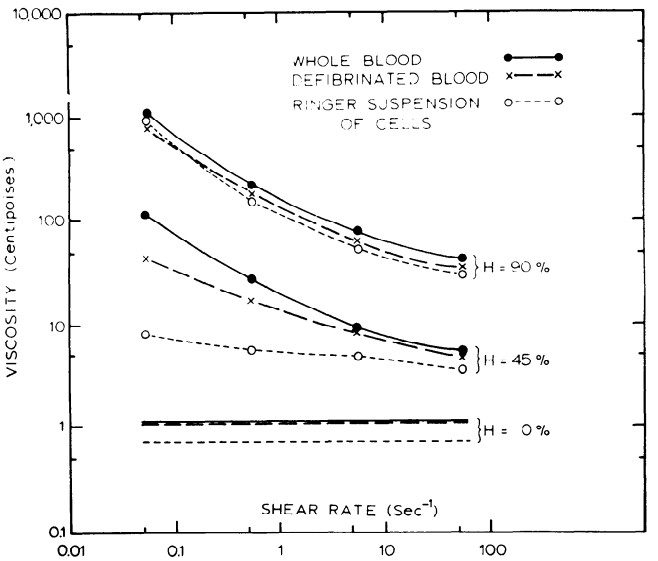

FIG. 3. Relationship between the logarithm of viscosity and the logarithm of shear rate for whole blood, defibrinated blood, and Ringer suspensions of cells at hematocrits (H) of 90 and 45%. The points were calculated from the regression equation (*equation 1*, Figs. 1 and 2). The lines marked H = 0 represent the data on plasma (solid line), serum (broken line), and Ringer solution (dotted line). Note the Newtonian behavior of the suspending media and the relative extents of departure from Newtonian behavior in the three blood systems at H = 45% and at H = 90%.

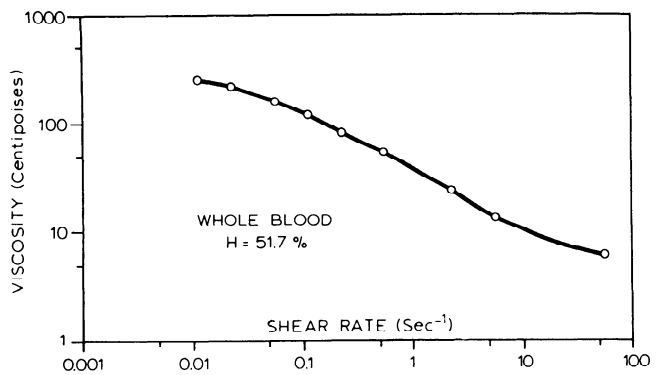

FIG. 4. Relation between the logarithm of viscosity and the logarithm of shear rate (down to 0.01 sec^{-1}) in a sample of whole blood.

cosities of the suspending media because similar differences are found even when relative viscosity values (viscosity of the suspension/viscosity of the suspending medium) are compared. With increasing H, the viscosities of defibrinated blood (Fig. 2*A*) and Ringer suspensions of cells (Fig. 2*B*) show increasingly pronounced dependence on shear rate and, at 90% H, the absolute viscosity as well as its dependence on shear rate are almost the same for all three systems. The similarity in the viscometric behaviors of whole blood, defibrinated blood, and Ringer suspension of cells at this high H is understandable since the differences among these three systems can be ascribed to the suspending media, which now occupy only small volume fractions. The non-Newtonian behavior of Ringer suspensions of cells at high H must be attributed to direct interactions among cells independent of cell-protein interactions. Since the viscometric behaviors of whole blood and Ringer suspensions of cells are similar at high H, the non-Newtonian behavior of whole blood at high H also appears to be due primarily to direct cell–cell interactions. From these results it can be concluded that at low H (less than 30%), the non-Newtonian behavior of whole blood is due to cell-protein interactions. As H is increased from 30 to 90%, the contribution of cell-protein interactions gradually becomes less important and cell–cell interactions become more influential. When H is close to 90%, the non-Newtonian behavior is due primarily to cell–cell interactions. Shear-rate dependences for viscosities of the various systems are shown more directly in Fig. 3 as log-log plots of viscosity versus shearrate at H values of 0, 45, and 90%. Plasma, serum, and Ringer solution (H = 0) are Newtonian, i.e., their viscosities are independent of shear rates. At 45% H, dependence of viscosity on shear rate is almost absent in Ringer suspensions of cells, moderate in defibrinated blood, and most pronounced in whole blood. At 90% H, the viscosities of all three systems are strongly and almost equally shear-rate dependent.

Changes in blood viscosity and shear stress as the shear rate approaches zero are important for ascertaining whether or not blood can sustain a yield stress before flow begins. As depicted in Fig. 3, down to a shear rate of 0.052 sec^{-1}, the viscosity of whole blood at normal H apparently shows a continually upward trend, suggesting the existence of a yield point. However, this suggestion is not supported by measurements made at still lower shear rates. In later stages of this investigation, viscosity measurements were successfully extended down to a shear rate of 0.01 sec^{-1}. The results on a whole blood sample with H of 51.7% are shown in Fig. 4. The log viscosity-log shear rate plot gives a sigmoidal curve tending to reach plateaus at both ends of the shear rates studied. Other investigators have found that, at sufficiently high shear rates (above 200–400 sec^{-1}), blood is similar to a Newtonian fluid with a constant, low viscosity (2, 25). The present experiments on shear rates down to 0.01 sec^{-1} suggest that at very low shear rates blood again approaches another Newtonian region with high viscosity. Between these two regions with approximately Newtonian behavior, there is a region with pronounced non-Newtonian behavior. This type of rheological behavior with flow approximating Newtonian in two regions of widely varying shear rates (18) has been observed for suspensions of butadiene-styrene copolymer latex (12, 13) and for solutions of macromolecules (19, 20). The shear rate at which the second approximately Newtonian region (low shear rates) begins varies in these systems. For whole blood, the $\log \eta - \log \dot{\gamma}$ curve begins its inflection below 0.1 sec^{-1} (Fig. 4). In the absence of measurements at lower shear rates, only the upward portion of the sigmoidal $\log \eta - \log \dot{\gamma}$ curve is observed (Fig. 3) and blood would have appeared to have a yield

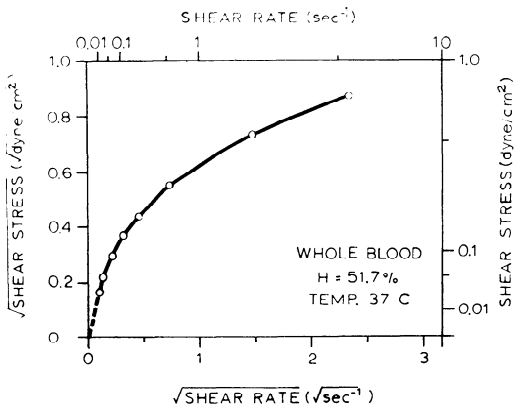

FIG. 5. Relationship between the square root of shear stress and the square root of shear rate in a sample of whole blood (same sample as in Fig. 4). Note the ever-changing slope pointing to the o,o origin.

point. In the presence of measurements down to a shear rate of 0.01 sec^{-1}, however, blood is seen to approach a region with constant viscosity. Therefore, at zero shear rate, the shear stress (viscosity $\times$ shear rate) also would be zero without a yield stress.

In order to study the changes in shear stress as the shear rate approaches zero, rheological data on blood often have been presented in the form of the square root of shear stress ($\tau^{1/2}$) versus the square root of shear rate ($\dot{\gamma}^{1/2}$) (5, 9, 14–16, 22), a plot in which the low ends of the coordinates are mathematically expanded for detailed examination. Such $\tau^{1/2} - \dot{\gamma}^{1/2}$ plot was first used by Casson (1) to estimate the yield stress in physical models in which particles form three-dimensional networks upon the cessation of flow. In the Casson model, a linear relationship exists between $\tau^{1/2}$ and $\dot{\gamma}^{1/2}$, and

$$\tau^{1/2} = \tau_y^{1/2} + b^{1/2}\dot{\gamma}^{1/2} \qquad (2)$$

In *equation 2*, $\tau_y^{1/2}$ is the intercept on $\tau^{1/2}$ — axis at zero $\dot{\gamma}^{1/2}$, and τ_y thus represents the yield stress of the system. As shown in Fig. 5, for whole blood, $\tau^{1/2}$ is not a simple linear function of $\dot{\gamma}^{1/2}$, a finding consistent with the observation of others (14, 22). The $\tau^{1/2} - \dot{\gamma}^{1/2}$ curve down to a shear rate of 0.01 sec^{-1} shows an ever-changing slope convexing to the $\tau^{1/2}$ axis, such that any reasonable extrapolation appears to pass through the origin (Fig. 5). Therefore, if measurements are made at sufficiently low shear rates, whole blood does not have a yield stress under the conditions of our experiments. Because whole blood does not have a linear $\tau^{1/2} - \dot{\gamma}^{1/2}$ relation, i.e., it does not fit the Casson model, one cannot ascertain the behavior of $\tau^{1/2}$ as $\dot{\gamma}^{1/2}$ approaches zero unless measurements are made at very low shear rates (e.g., down to 0.01 sec^{-1}). In the absence of such low shear-rate measurements, one may get the impression that the terminal portion of the $\tau^{1/2} - \dot{\gamma}^{1/2}$ plot is linear. If a linear extrapolation is made for such a short portion of the $\tau^{1/2} - \dot{\gamma}^{1/2}$ curve, an apparent "yield stress" would be obtained (5, 9, 14–16, 22). Under the conditions of our experiments, whenever measurements are made down to a shear rate of 0.01 sec^{-1}, $\tau^{1/2} - \dot{\gamma}^{1/2}$ plots of all blood systems with H values in the normal range show the same tendency of going through the origin. With blood systems containing very high cell percentages (e.g., H = 90%), the steepness of the $\tau^{1/2} - \dot{\gamma}^{1/2}$ slope increases rapidly as $\dot{\gamma}$ is reduced to 0.01 sec^{-1}. In these cases, measurements at shear rates even lower than 0.01 sec^{-1} are needed to ascertain whether or not the $\tau^{1/2} - \dot{\gamma}^{1/2}$ curve would go through the origin.

In spite of our findings that blood has no yield stress and that its rheological behavior is not in accordance with the Casson model, the $\tau^{1/2}$ and $\dot{\gamma}^{1/2}$ data at two shear rates (0.52 and 0.052 sec^{-1}) have been fitted to the Casson equation (*equation 2*). Extrapolation of a straight line connecting these two points to zero shear rate gives an intercept $\tau_e^{1/2}$ (subscript e is used instead of y as in equation 2). This is done for two reasons: *1*) to compare our results with those of other investigators (e.g., 16) who have used the Casson equation to analyze their rheological data, and *2*) to gain an empirical, though arbitrary, measure of the degree of departure from Newtonian behavior for various systems. The τ_e values thus calculated can be correlated with H. For whole blood and defibrinated blood, with H up to 80% (Fig. 6*A*), the following empirical equation (17) holds:

$$\tau_e^{1/3} = a(H - b) \qquad (3)$$

Equation 3 obtained by the least-squares method for our data on whole blood (Fig. 6*A*) agrees substantially with the results of other investigators (16), though the latter found the equation applicable only up to approximately 50% H. At high H values, the relation between τ_e and H is better described by another empirical equation (24, Fig. 6*B*).

$$\tau_e = e^{aH+b} \qquad (4)$$

The H values at which τ_e becomes appreciable are approximately 3% for whole blood, 20% for defibrinated blood, and 30–40% for Ringer suspensions of cells (Fig. 6*A*). These values are approximately the hematocrits at which non-Newtonian behavior first appears with increasing H (Figs. 1, 2*A*, and 2*B*). It is also indicated in Fig. 6*A* that, up to the normal H range, the τ_e in whole blood is primarily due to the presence of plasma proteins (especially fibrinogen), which interact with the cells. When H is progressively increased, the τ_e values for the three systems (whole blood, defibrinated blood, and Ringer suspensions of cells) become close to one another, indicating the predominance of cell-cell interactions over cell-protein interactions. Thus the relative contributions by these two types of interactions to the empirical value τ_e are similar to their relative contributions to the non-Newtonian behavior of whole blood (see the first paragraph of RESULTS AND DISCUSSION). If contributions of cell-cell interactions and cell-protein interactions are taken as additive, an oversimplification

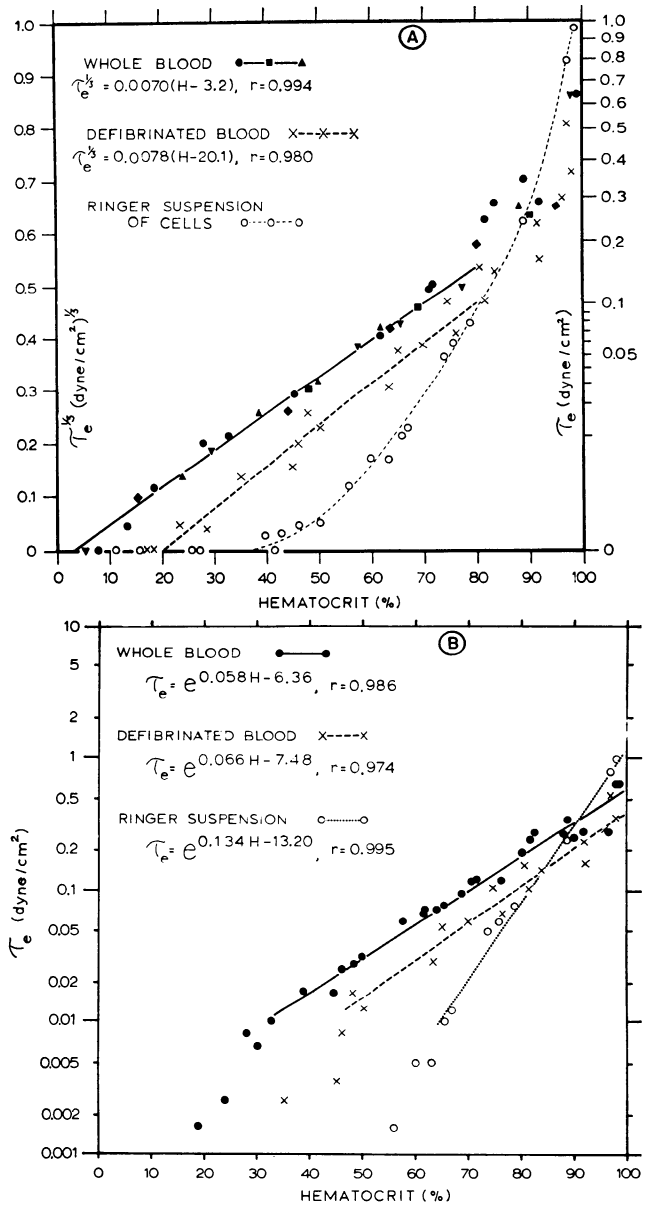

FIG. 6. *A:* relationship between the cube root of τ_e and the hematocrit. For whole blood, a different closed symbol is used for the results obtained on each of five subjects. The linear regression formulae and the coefficients of correlation (r) for whole blood and defibrinated blood (both up to 80% H) are given in the graph. The results on Ringer suspensions of cells show a curvilinear relationship. *B:* relationship between the logarithm of τ_e and the hematocrit for whole blood, defibrinated blood, and Ringer suspensions of cells. Note the linearity of the results when τ_e is higher than 0.01 dyne/cm² (whole blood H > 32%, defibrinated blood H > 47%, and Ringer suspension H > 65%). The linear regression formulae and the coefficients of correlation (r) are given in the graph.

necessary to breach the problem, their relative contributions to whole blood τ_e can be calculated. Thus τ_e of Ringer suspensions of cells is assumed to represent cell-cell interactions; τ_e of whole blood, the sum of two types of interactions; and the difference between the two τ_e's, cell-protein interactions. Figure 7 shows the relative

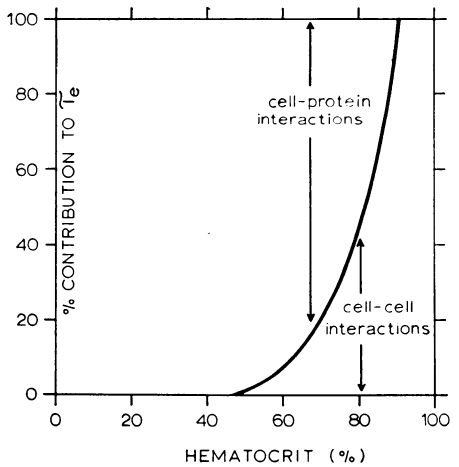

FIG. 7. Relative contribution of cell-protein interactions and cell-cell interactions to τ_e. The percent contribution of cell-cell interactions is calculated from 100 (τ_e of Ringer suspension/τ_e of whole blood). The percent contribution of cell-protein interactions is calculated from 100 (τ_e of whole blood − τ_e of Ringer suspension)/(τ_e of whole blood). Note that cell-protein interactions constitute the major contributing factor up to a normal hematocrit range and that cell-cell interactions become progressively more important as the hematocrit is raised beyond the normal range.

contributions of cell-cell and cell-protein interactions to the τ_e of whole blood thus calculated. This figure may also be taken as an approximate measure of the relative contributions of cell-cell and cell-protein interactions to the departure of rheology of whole blood from Newtonian behavior. At H higher than 90%, the τ_e value of Ringer suspensions of cells are greater than those for whole or defibrinated blood, indicating that τ_e values are not simply additive. At these high H values, the viscosities of Ringer suspensions of cells are also higher than those for whole or defibrinated blood. It seems that proteins aid flow at such high H, possibly due to an increase of deformability of cells or through some lubrication mechanism.

In determining blood viscosity at shear rates lower than 1 sec^{-1}, Cokelet et al. (5) found a decay of the torque-time curve and attributed this to the development of a plasma layer; therefore, they have used grooved cups and rotors. Nevertheless, a decay of torque with time, though less rapid, was still observed. Since it has not been proved that the plasma layer is the cause for the torque decay, the introduction of further instrumentational complication by grooving the cup and the rotor seems unnecessary. In fact, Merrill et al. (16) have suggested that under certain conditions a plasma layer may be formed even in the grooved system to isolate the blood in the grooves from the remainder of the blood. Even if the formation of a plasma layer were the correct explanation for the torque decay, the grooved cylinder surfaces would still not be better than the smooth surfaces in simulating the interior surfaces of blood vessels which do not possess regular grooves. In the present experiments, when a time-decay of torque was observed

at low shear rates, the maximum (peak) value was used to calculate shear stress and viscosity. The extrapolation technique used by Cokelet et al. (5) was not followed for two reasons: first, the decay is not a simple function of time and is therefore difficult to extrapolate, whereas the maximum torque reading is a reproducible value; second, there is no theoretical basis for extrapolating the torque curve back to zero time. It would seem more reasonable to use the low plateau to which torque has decayed. Despite our use of smooth rather than grooved cylinders and our use of the maximum rather than the extrapolated torque readings, the empirical τ_e values obtained for whole blood in the present experiments agree well with the "yield stress" values obtained by Merrill et al. (16).

As pointed out in the beginning of this paper, low shear rates and non-Newtonian flows exist in the circulation, therefore an understanding of the factors contributing to the non-Newtonian behavior of blood has obvious significance in circulatory physiology. Our results indicate that the non-Newtonian behavior of blood at normal hematocrits results primarily from cell-protein interactions (e.g., formation of cell aggregates at low shear rates) rather than direct cell-cell interactions. The question of whether or not blood has a yield stress which must be exceeded before the initiation of flow is also of physiological importance, since this determines the ease with which circulation can be restarted following a period of flow cessation. The results of our shear-stress measurements at low shear rates indicate the absence of a yield stress, but the dependence of such measurements on time deserves further investigations.

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