Table 1. Elastic stiffness coefficients and technical elastic moduli of bone. Units used: C_{11}, C_{12}, C_{13}, C_{33}, C_{44}, Young's moduli (axial and transverse), and shear moduli (axial and transverse) are expressed in 10^{11} dynes per square centimeter; compressibility in 10^{-11} square centimeter per dyne; Poisson's ratios are dimensionless.

Elastic parameter	Dried phalanx	Dried femur	Fresh phalanx
C_{11}	2.12 ± 0.07*	2.38 ± 0.14	1.97 ± 0.05
C_{12}	0.95 ± .03	1.02 ± .06	1.21 ± .04
C_{13}	1.02 ± .14	1.12 ± .21	1.26 ± .12
C_{33}	3.74 ± .16	3.34 ± .12	3.20 ± .11
C_{44}	0.75 ± .02	0.82 ± .02	0.54 ± .01
Young's modulus (axial)	3.05	2.60	2.20
Young's modulus (transverse)	1.59	1.79	1.13
Shear modulus (axial)	0.75	0.82	0.54
Shear modulus (transverse)	.65	.74	.45
Compressibility	.688	.633	.649
Poisson's ratio, μ_{12}†	.365	.321	.482
Poisson's ratio, μ_{13}	.334	.330	.397
Poisson's ratio, μ_{31}	.174	.228	.204

* The standard deviations of the values are given and are based on a statistical analysis in which it was assumed that the standard deviation in the measurement of a velocity was 3 percent and that the error in orientation of a sample was 5°. † Axes 1 and 2 are in the transverse plane; axis 3 is parallel to the bone axis.

propagated in specific directions in rectangular-parallelepiped shaped bone samples (*11*). The specimens used were dried samples of bovine femur and phalanx and fresh samples of phalanx. The dried materials were prepared by degreasing the bones in toluene, then drying them in a vacuum oven at 35°C. However, during the course of the experiments, the material was permitted to equilibrate with the moisture of the atmosphere. The fresh materials were immersed in a standard saline solution at all times except when measurements were being made. Opposite faces of the samples were flat and parallel within 12 μ and were polished. The ultrasonic velocities were determined by measuring the time of transit of ultrasonic pulses through the material. Samples were placed between two piezoelectric transducers, and the transmitting transducer was excited by a 1-μsec pulse from a 1.5 kv pulser. The transmitted signal was detected by the receiver transducer and was amplified by a two-stage, wideband amplifier. The time measurement was obtained by means of a 0- to 100-μsec delay potentiometer and an electronic time interval counter. The velocities were calculated from the transit times and the physical dimensions of the specimens.

The calculated elastic stiffness coefficients of the three types of material are presented in Table 1. The values in the table are based on the averages of 24, 24, and 36 measurements in different directions on five, six, and seven specimens of dried phalanx, dried femur, and fresh phalanx, respectively. All specimens of one type were cut from a single bone.

It is possible to calculate from the elastic stiffness coefficients all of the technical elastic moduli, such as the Young's modulus, shear modulus, Poisson's ratio, and the bulk compressibility (*12*). The first two moduli are functions of direction; their values in the axial and in the transverse bone direction are also given in Table 1. The three independent Poisson's ratios are given.

The technique used here is a relatively simple one. It may be applied to other studies of the elastic properties of bone in which variables such as type of bone, diet, and age of animal are considered.

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Fluid Drop-Like Transition of Erythrocytes under Shear

Abstract. *Red cells dispersed in a continuous medium of high viscosity possess the flow properties of fluid drops. The cells at rest are biconcave, while under shear they become progressively deformed into prolate ellipsoids, their long axis aligned parallel to the flow direction. The red cell membrane rotates around the hemoglobin like a tread of a tank. At high rates of shear this mechanism greatly reduces viscosity at all hematocrit values.*

The critical importance of red cell deformability to the flow properties of blood has recently been emphasized by several investigators (*1–4*). Their evidence has uniformly suggested that the deformability of the red cell is a major determinant of the shear thinning properties of blood at high rates of shear. The exact manner by which red cell deformability facilitates flow has not been established. Dintenfass (*1*) suggested that the membrane of the red cell under shear is subjected to liquefaction and gelation, thus allowing transmission of shear stress into the interior of the cell. Goldsmith (*2*) found the flow characteristics of red cells in tubes comparable to those of deformable liquid drops. In studies with packed cells in our laboratory (*5*) it was observed that the membrane actually rotates around the cell contents. All these concepts suggest that the red cell, when subjected to shear, assumes the flow properties of a fluid drop. Consequently, whole blood might thus be compared to an emulsion of hemoglobin droplets dispersed in plasma rather than a suspension of particles. This assumption has been tested in model experiments along the lines of emulsion rheology. As shown by Taylor (*6*), the viscosity of emulsions (η_s) is not only a function of the viscosity of the continuous medium (η_0) and the volume fraction (H) of the suspended phase but is strongly influenced by the ratio of the viscosities of suspended droplets (η_i) and continuous phase where

$$\eta_s = \eta_0(1 + 2.5H)\frac{(\eta_i/\eta_0 + 0.4)}{\eta_i/\eta_0 + 1} \quad (1)$$

This equation originally applied to dilute emulsions at high rates of shear (capillary viscometers). To test the assumption of red cell fluidity under shear, erythrocytes were immersed at various concentrations in highly viscous solutions and the viscosity of these "suspensions" was measured at both high and

low rates of shear. A transparent cone plate viscometer (rheoscope) (*7*) allowed the direct microscopic study of the influence of shear upon the individual erythrocytes.

Human venous blood was drawn from healthy donors; a mixture of citrate, phosphate, and dextrose (CPD) (67.5 ml of CPD to 450 ml of blood) was added to prevent coagulation; identical results were obtained when heparin and ethylenediaminetetraacetate were used as anticoagulants. The cells were separated from the plasma and the buffy coat after centrifugation, then washed three times in isotonic buffered saline, and centrifugally packed to a concentration of 98 ± 1 percent (4000*g* for 30 minutes). Solutions of dextran with an average molecular weight of 40,000 were prepared as 35 percent concentrations in distilled water. The osmolarity of this solution was adjusted so that added erythrocytes showed neither swelling nor shrinking when observed in a phase microscope (*8*). The cells were counted in a Coulter electronic particle counter. Viscosities were measured in a GDM-viscometer (*9*) at shear rates between 0.1 and 20 sec^{-1} as well as in a Wells-Brookfield microviscometer (10X LVT) (with a transparent cone and plate) (*7*) capable of measuring shear stresses up to 233 dyne/cm^2 and at shear rates between 1.15 and 230 sec^{-1}. When Newtonian test fluids (Cannon Instrument oils, Nos. S6 and S20) were checked, both instruments agreed within ± 5 percent at all rates of shear.

The 35 percent dextran solution had a viscosity of 62 centipoise at all shear rates. When packed red cells were added to make a volume fraction (hematocrit) of 50 percent the viscosity at 0.1 sec^{-1} was 525 centipoise. Viscosity fell with increasing shear rates until a value of 61.2 centipoise at 230 sec^{-1} was obtained. At this rate of shear this viscosity value was equivalent to that of the cell-free dextran (Fig. 1). The red cells suspended in this viscous dextran were observed microscopically in the rheoscope (*7*) where the cells at rest showed a typical biconcave shape, all cells being monodispersed. At a shear rate of 1.15 sec^{-1} the moving cells were undistorted and only occasionally tumbled during flow. At 2.3 sec^{-1}, the red cells, still largely biconcave, began to align themselves parallel to the direction of flow with less tumbling; and at 11.5 sec^{-1}, the cells began to be deformed into prolate ellipsoids with their long axes parallel to the direction of flow (Fig. 2). No tumbling was observed, but the red cell membrane was seen to exhibit a rotatory motion with undulating waves in the surface. The deformation and orientation of the red cells produced an appearance similar to that of a school of fish. When the rate of shear was further increased, the cells were even more elongated. At these high rates of shear, stroboscopic photomicrographs showed alignment of all the deformed red cells with their long axis parallel to the circular direction of flow. Orbiting was never observed. Upon sudden stoppage of the flow, the red cells immediately resumed their biconcave shape, whereas a gradual decrease in rate of shear resulted in shorter and shorter ellipsoids until at zero shear rate the cells showed their biconcave resting shape.

Comparison of the viscosity profiles of red cells in highly viscous dextran, hematocrit range 10 to 90 percent, showed that increasing volume fractions of red cells increased viscosity only at low velocity gradients. At high rates of shear (230 sec^{-1}) the viscosity was independent of red cell concentrations up to 50 percent and rose but slightly at 75 and 90 percent. Increased cell numbers resulted in high viscosity near stasis accompanied by greater shear thinning (Fig. 1), that is, progressive reduction in viscosity with increasing shear rate.

These microscopic and viscometric results clearly indicate that mammalian red cells are capable of assuming the properties of a fluid drop under shear, as has been postulated by several authors (*1, 2, 4*). The physical features of the normal erythrocytes at rest, as elaborated by Fung (*10*), Katchalski (*11*), Rand (*12*), and others, permit such a transition. The cell can be considered to be a flexible shell, incompletely filled with an incompressible viscous fluid (*10*). The membrane is known to be highly bendable, but in spite of the low bending rigidity there is considerable extensional rigidity (*11, 12*). Most contemporary authors (*13*) agree that there is no stroma to support the typical biconcave resting shape of the erythrocyte; however, as the biconcave shape results in an incomplete filling of the membrane shell, the red cell can be deformed isochorically, that is, without change in surface area or volume, into an infinite variety of shapes (*10*). When subjected to a uniform shear field, the red cell, as seen here, is deformed into a prolate ellipsoid. As observed microscopically this deformation is accompanied by both an orientation of the cell in the shear planes and a rotational motion of the cell membrane around its contents, which resembles the rotation of the tread of a tank around its wheels. This corresponds to the behavior of an ordinary fluid drop when subjected to a uniform shear field. As described by Taylor (*6*) and by Rumscheidt and Mason (*14*), such deformation is the consequence of tensile and compressive forces to which a fluid

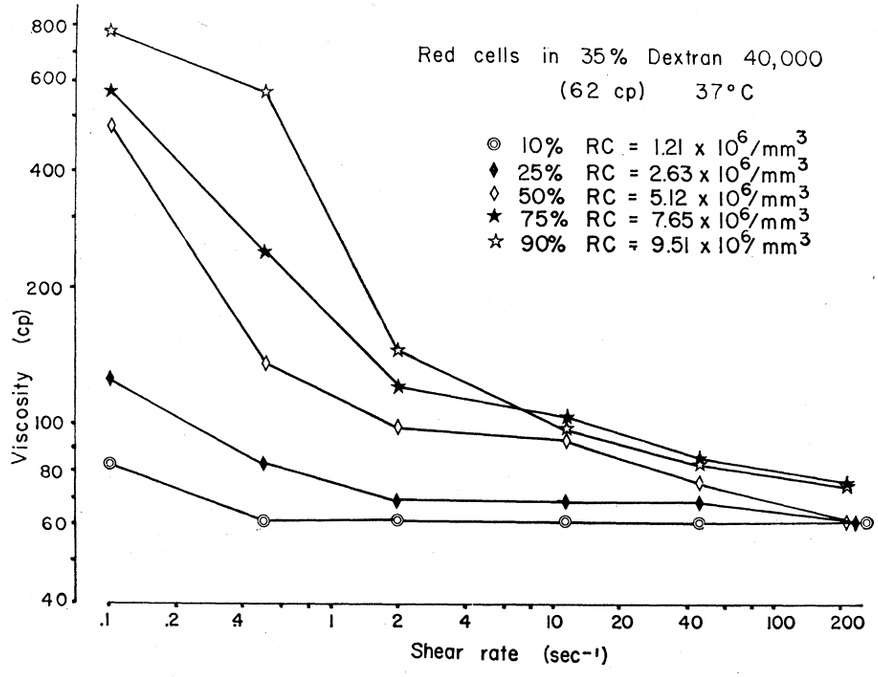

Fig. 1. Viscosity profiles of human red cells dispersed in 35 percent dextran (molecular weight, 40,000) at different red cell fractions; cp, centipoise.

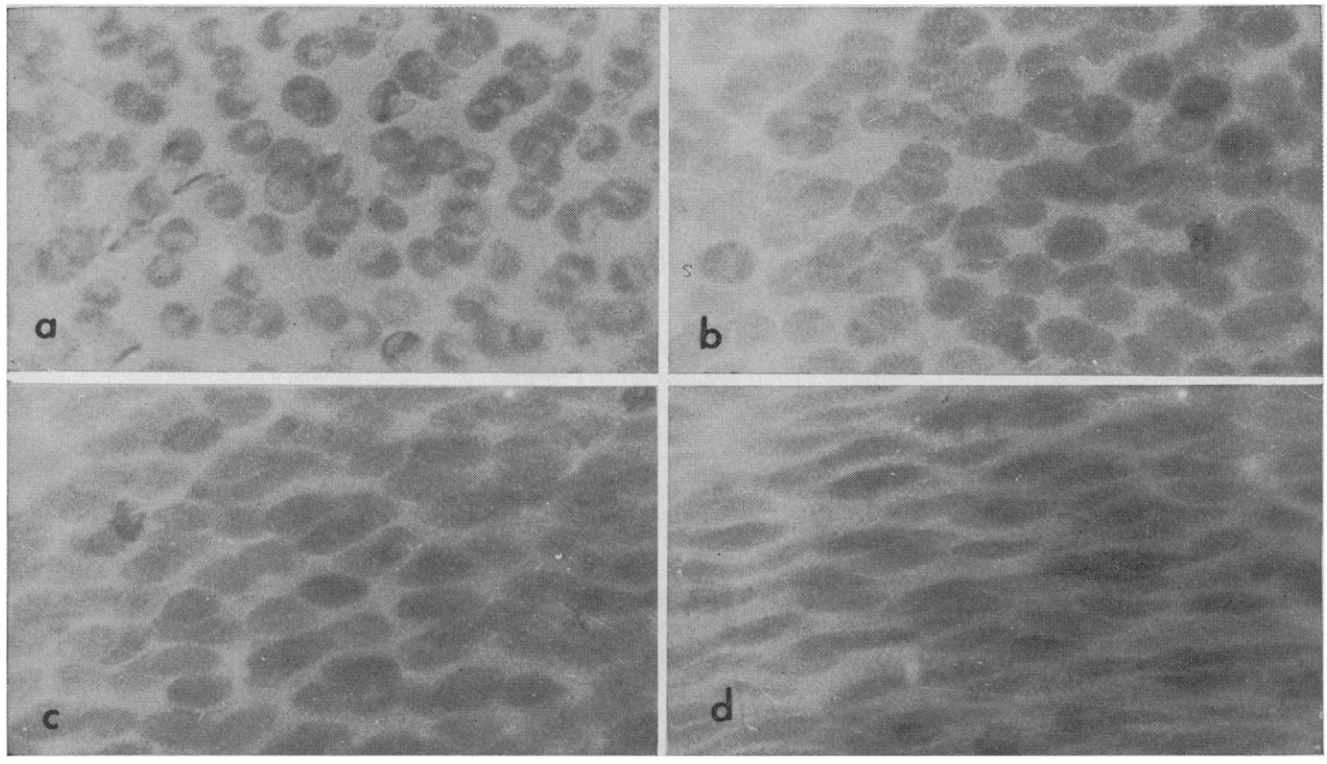

Fig. 2. Human red cells dispersed in highly viscous medium and flowing at different rates of shear. Strobe photomicrographs taken in a transport cone and plate viscometer. Cells at rest (a) and at 11.5 sec^{-1} (b), 46 sec^{-1} (c), and 230 sec^{-1} (d) rates of shear.

drop is subjected in alternate quadrants when placed in a uniform shear field. The deformation (D) of ordinary fluid drops has been defined by Taylor (*6*) as follows:

$$D = \frac{L-B}{L+B} = G \cdot \eta_0 \cdot \frac{b}{\theta} \frac{(19\,\eta_1/\eta_0 + 16)}{(16\,\eta_1/\eta_0 + 16)} \quad (2)$$

where L and B represent length and breadth of the ellipsoid; b, the radius of the sphere; θ, the interfacial tension; and G, the incident rate of shear.

In the case of one liquid suspensed in another, the interfacial tension results in a spherical shape (radius b) of the liquid droplet at rest; deformation of the drop is possible only at the expense of an increase in surface area and of an increase in the surface tension. In contrast to this, the red cell can be deformed without an increase in membrane area, an important consequence of its biconcave shape (*10*). This strongly facilitates the progressive deformation of the red cell with increasing shear rate, as predicted by Eq. 2. Experiments in this laboratory have shown that a similar deformation takes place in blood with a high hematocrit value at low rates of shear and with normal hematocrit at high rates of shear.

The deformation of red cells into prolate ellipsoids and the alignment of the cells, with their major axes parallel to the direction of flow, would probably lead to reduced viscous hindrance (*15*). The most important rheological phenomenon observed here, however, is not deformation but rather the rotational motion of the red cell membrane. This permits a transmission of the external shear stresses across the membrane and is likely to result in an inner circulation of the hemoglobin so that the red cell participates in flow rather than distorting it.

Cell deformation, orientation, and rotation increase with rising rates of shear. At the same time reduction in apparent viscosity is observed. In the absence of cell aggregation, this fall in apparent viscosity suggests that transmission of shear is taking place. Under the present experimental conditions, at low rates of shear, the red cell remains largely undeformed where the viscosity is principally a function of the volume fraction of the red cells. Near stasis, therefore, the presence of cells influences the viscous resistance of the suspension. With increasing rates of shear, however, the viscosity falls progressively and becomes virtually independent of hematocrit at 230 sec^{-1}. This striking behavior is incompatible with the assumption that the red cells behave like suspended particles; in this case, the viscosity would strongly rise with hematocrit and the suspension would turn into a solid at hematocrit values in excess of 60 percent.

The present data, therefore, strongly suggest that the rotation of the membrane is actually accompanied by an inner circulation of the hemoglobin as established for deformable drops. The present model experiments are supplemented by microrheological studies with packed red cells and red cells in ghost-plasma suspensions in which a similar tank-tread motion was observed (*5*). These studies showed that the erythrocyte behaves like a fluid drop without change in the physical characteristics of the membrane. The hematological and hemodynamic consequences of these results obviously require further elaboration. The present results, along with the bulk of evidence from this laboratory (*4*, *5*, *7*) and Goldsmith's (*2*), support the earlier hypothesis (*3*, *4*) that the non-Newtonian viscosity of blood is based upon at least two distinct mechanisms: (i) The aggregation of erythrocytes into a three-dimensional structure of rouleaux gives rise to an increase in apparent viscosity with decreasing rate of shear and the existence of a yield shear stress; and (ii) the deformation of the red cells and their transition into fluid drops produce the shear thinning characteristics of blood at

high rates of shear, especially in narrow tubes (*2*). Since the blood circulating through the vasculature is subjected to both high and low rates of shear, both phenomena are of hemodynamic significance.

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Renin-Aldosterone System in Parkinson's Disease

Abstract. *Low blood pressure is frequent in the akinetic form of Parkinson's disease. A low renin activity in plasma as well as a low rate of aldosterone secretion is demonstrated in these patients. Renin activity in the plasma is further decreased by treatment with* L-*dihydroxyphenylalanine, thus partially accounting for the hypotensive episodes seen with this form of therapy.*

Patients with Parkinson's disease, a chronic disorder of the nervous system appearing in later life, often have a blood pressure lower than the mean for their age group. This relatively low blood pressure, present particularly in the akinetic form, is more evident in the standing position and contributes to a chronic state of fatigue and to occasional episodes of postural dizziness. The experimental treatment of these patients with the dopamine precursor L-dihydroxyphenylalanine (L-dopa) can lead to an exacerbation of hypotension to degrees that may become alarming (*1*).

Numerous studies have established a role for the renin-aldosterone system in regulation of blood pressure and in various forms of hypertension (*2*). There is considerable evidence for the participation of the sympathetic nervous system in the control of blood pressure (*3*) and of renin release (*4*). Recently, a defect in the sympathetic nervous system has been postulated in essential postural hypotension (*5*), as it had been in Parkinson's disease. We therefore studied the state of the renin-aldosterone system in the latter illness.

Renin activity in the plasma was determined by the method of Boucher *et al.* (*6*) in 35 normotensive control subjects, 8 of whom had been under a metabolic diet of 135 meq of sodium per day for 3 days before the blood sampling (*7*). Similar determinations were carried out in 31 patients with Parkinson's disease (mean age, 62.1 years) with a mean duration of illness of 9.7 years. Eleven patients were taking anticholinergic medication, but the remainder were not receiving drugs at the time of renin determination. All subjects were recumbent at time of sampling (after 12 hours of rest). Under an unrestricted salt intake, the plasma renin activity was significantly lower in patients than in controls ($P < .01$) (Table 1). This difference persisted when 17 of these patients were given a diet of 135 meq of Na per day (K, 90 meq/day) for 3 days before determination of renin activity ($P < .01$). Of the 48 measurements made, only 9 were above 5 ng liter^{-1} min^{-1}, and 28 had undetectable amounts.

Five Parkinsonian patients were chosen consecutively for more detailed studies. That the subgroup is representative of the larger group is evidenced by the fact that these three men and two women had a mean age of 63.2 years; a plasma renin activity under unrestricted salt intake of 2.2 ± 1.6 ng liter^{-1} min^{-1} and under a Na diet (135 meq) (K, 90 meq/day) of 3.6 ± 1.7 ng liter^{-1} min^{-1} was observed. Kidney functions were normal for that age range (blood urea, 27.6 ± 4.9 mg per 100 ml of blood; creatinine clearance, 82.4 ± 13.8 ml/min). Hemoglobin (15.4 ± 0.6 g), hematocrit (43.1 ± 1.6 percent), blood sodium (140.5 ± 0.7 meq/liter), blood potassium (4.4 ± 0.2 meq/liter), and Bromsulphalein test (4.9 ± 0.8 percent) were all normal, as were the individual and mean blood pressure (20 determinations per patient) in both the standing (mean, 121/78 mm-Hg) and recumbent positions (mean, 133/83 mm-Hg). Total blood volumes, red blood cell volumes, and plasma volumes were normal in all five cases with the exception of a slight (8.8 percent) decrease in plasma volume in a single patient.

Table 1. Plasma renin activity in Parkinson's disease and in normotensive healthy control subjects expressed in nanograms of angiotensin liberated per liter per minute (mean ± S.D.); *N*, number of patients.

Na diet	*N*	Angiotensin (ng liter^{-1} min^{-1})
	Control	
Unrestricted	27	9.5 ± 6.7
135 meq/day	8	9.8 ± 12.9
	Parkinson	
Unrestricted	31	2.4 ± 4.1
135 meq/day	17	2.7 ± 2.7
	Parkinson subgroup	
Unrestricted	5	2.2 ± 3.6
135 meq/day	5	3.6 ± 3.9

Amounts of aldosterone in plasma were measured in these five patients by the method of Nowaczynski *et al.* (*8*). With this method the normal mean for peripheral plasma aldosterone is 8.09 ± 1.08 ng/100 ml (diet: Na, 135 meq/day; K, 90 meq/day) with a range of 2 to 16.6 ng/100 ml. Plasma aldosterone was within the normal range in four of our five patients and elevated in one (Table 2). The secretory rate of aldosterone was determined by the double isotope dilution method (*8*). ^{3}H-Labeled aldosterone (2 μc at a specific activity of approximately 100 μc/μg) was injected into the antecubital vein. Normal range is from 50 to 210 μg of aldosterone per day secreted. The secretion was at the lower limits of normal range (Table 2). Thus in Parkinson's disease aldosterone secretion and renin activity vary in parallel, and one can rule out conditions of primary or secondary hyperaldosteronism.

In most cases of akinetic Parkinson's disease, dopamine excretion in the urine is low (*9*). This was also the case for four out of five cases in the subgroup under study (Table 2). Adrenaline values were within normal limits, but two of the patients had low noradrenaline excretion. All had low homovanillic