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ON BIORHEOLOGY* JOINT PLENARY LECTURE

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IN MY Inaugural Address this morning [1] I gave a brief historical account of biorheology as an organized science. The different fields of biorheology, including hemorheology [2-4], have grown rapidly and to such an extent that any abridged survey will remain inadequate. I shall therefore not give a survey on the development and present status of different fields of biorheology. However, I should like to draw your attention to a book on biorheology which our colleague SCOTT BLAIR is writing now. It will be published some time next year in Amsterdam [5].

We are all interested in the future prospects of biorheology and, therefore, I shall now make a few comments on them. These future prospects concern both the medical and biological sciences.

In addition to the study of hemorheological diseases or pathological conditions, such as thrombosis, circulatory shock or sickle cell anemia, there are many other fields of great practical significance which are arousing interest: among them, there are the effects of different shock stresses on the brain. They are of concern to the neurologist and others in comparing injuries arising from heading a football or to glancing blows such as often occur in car crashes, both in racing and on the roads. The study of rheological properties of bone, skin, cartilage, among others, is important. With regard to the world population, research on better contraceptive medication, not having risks inherent nor side effects, suggests that much further work is required on cervical mucus and on semen. The remarkable and unique type of elastic behavior associated with muscle is now being intensively studied in relation to biochemical investigations. Rheumatic and bronchial diseases are associated with different rheological properties of synovial fluid and of bronchial mucus, respectively.

Much more work is needed in botany. Recent work of several investigators suggests that the transport of phloem [6] presents important rheological problems.

Our colleague VOROB'EV [7] has recently pointed out the importance to study not merely the rheology of cytoplasm, but of individual intracellular structures, especially those of nuclei, chromosomes and cell membranes. He also emphasized that our knowledge of the behavior of biological macromolecules has been usually limited to studies of dilute solutions.

* For abstract of this Lecture see *Biorheology* 9, 141, 1972.

As VOROB'EV [7] puts it: "The interest in intermolecular interactions was aroused in connection with the discovery of the possibility of spontaneous regular association of macromolecules, which occurs under appropriate conditions in concentrated solutions. In some cases under strictly determined conditions, even self-assembly of certain biological structures—ribosomes and membranes, viruses and phages—from molecules of proteins, lipids and nucleic acids can be performed".

There can be little doubt that the advances in cytology linked to biorheological studies will benefit cancer research.

Biorheology becomes more and more concerned with the explanation of the nature of biorheological processes. This is done with the use of rather complicated theoretical approaches and models, but in the practice of medicine the usefulness of such an approach depends on the extent of our comprehension of the structural and chemical basis of biorheological phenomena.

There is a continuous expansion in the development of biorheology as an independent biological science.

The numerous deformations inherent in embryonal development await rheological study and interpretation. Concomitant with such future studies, embryology as well as genetics will be more and more related to biorheology.

In so far as psychology may be regarded as a branch of biology, "psychorheology" must be included in biorheology. The term "psychorheology" was proposed by SCOTT BLAIR and COPPEN [8] to describe the study of the relation between the assessing of rheological properties by handling materials (mainly food stuffs) and their measurements by means of physical apparatus. These studies are fully described in SCOTT BLAIR'S "Introduction to Industrial Rheology" [9].

It was at the IV. International Congress on Rheology, that KATCHALSKY gave an account on what he termed mechanochemistry [10]. HE [11], KUHN [12], BREITENBACH and KARLINGER [13] found independently in 1948 that many swollen macromolecular substances can convert under isothermal conditions chemical energy directly into mechanical work. Mechanochemistry, a field of great importance to biorheology, is especially significant in relation to the contraction and relaxation of muscles.

The motility of animals, which depends on the direct conversion of chemical into mechanical work, has been one of the riddles of science. With the introduction of chemical thermodynamics by GIBBS [14] as an integral part of physical chemistry, it became possible to appreciate the coupling of metabolic processes with the motility of living organisms. However, the thermodynamics of "open" systems also had to be introduced and KATCHALSKY wrote with CURRAN an important book on this subject [15]. They pointed out the differences between adiabatic, closed and open systems. Open systems are enclosed by walls that allow exchange of both matter and energy with the surroundings. Open systems are therefore of particular significance for the understanding of biological phenomena, since living organisms exchange constantly both matter and thermal energy with their external environment. Katchalsky and Curran considered flows and forces in the thermodynamics of irreversible processes. Scalar flows, with no direction in space, are mainly those concerned with chemical reactions, while directed flows, characterized by vectorial properties, vary in nature and include, among others, flows of diffusion, electric current and heat. More complex cases, such as viscous flows, have been omitted in their treatment of many biophysical phenomena. However, it appears that nonequilibrium thermodynamics will be also of growing importance to the advancement of biorheology.

In his presentation on abnormal phenomena of flow, given at the I. International Congress on Rheology in 1948, WEISSENBERG referred to thermodynamic analysis [16]. He proposed that the expanded amount of energy in every differential interval of time, when a material passes under some mechanical action through various rheological states, may be divided into two component parts. One part is completely reversible into external work, while the other is completely irreversible. Weissenberg suggested the construction of networks which exhibit an analogous division of the expanded amount of energy into reversible and irreversible components and considered these components as well as the modes of interconnection "to be of greater complexity than can be envisaged in the conventional picture of networks".

It was about 20 years later that KATCHALSKY began to develop the concept of "network thermodynamics" for living systems, in particular for biological membranes (17). I recall his great enthusiasm with which he envisaged the application of network thermodynamics to biorheology. This was last May, when he phoned me from Boston, just prior to my departure from New York for Lyon, where I had to participate in a meeting concerning the organization of our two Congresses. He planned to present his thoughts on biological membranes, thermodynamics and biorheology in a Plenary Lecture at our Congress tomorrow. We shall never be acquainted with some of these thoughts. As I mentioned this morning in my Joint Plenary Address, tomorrow's Plenary Sessions, where he wanted so much to be with us, will be dedicated to his memory.

I come now to the presentation of experimental findings from two areas of hemorheology in which my associates and I have been involved during the past few years. I believe that the presentation of these findings is not merely of interest to workers in hemorheology or biorheology, but may be of concern also to rheologists not acquainted with biological problems.

One area of work [3, 18–20], in which HUANG and KING participated, comprises flow properties of blood at minimal shear rates. The other area of our work [21–25], in which I was assisted by KING, deals with viscous resistance and viscoelastic properties [26] of surface layers of plasma proteins.

I shall deal first with the flow properties of whole or non-diluted human blood at varying shear rates from 1000 down to 0.0009 sec^{-1} .

In 1942, COPLEY *et al.* [27] found that blood exhibits non-Newtonian behavior and suggested that it might possess a yield stress. At that time there was no suitable instrumentation for studying the rheological behavior of blood at very low rates of shear. In recent years, a number of investigators have studied blood viscosity down to a shear rate of 0.01 sec^{-1} [28–30]. Their claims, that blood has a yield stress, were not substantiated under rigorous conditions.

There is considerable discussion in the literature regarding the significance of viscosity measurements at minimal shear rates, when the viscosity of blood increases markedly [3, 18, 28–30]. Physiologically, this occurs in the circulation preceding stasis or cessation of blood flow in the postcapillary vessels of the microcirculation and after the resumption of blood flow. Low velocities of blood flow exist particularly in pathological conditions, such as circulatory shock and inflammation, as well as during surgical operations, including the transplantation of the heart and other organs or the implantation of prosthetic devices in the macrocirculation [31, 32]. Thus, although there is considerable debate in the literature on the value of blood viscosity measurements at minimal shear rates, it is evident that such studies are relevant to the practice of medicine and surgery. We decided, therefore,

to investigate the flow properties of blood down to a rate of shear of 0.0009 sec^{-1} [3, 18-20].

Our first findings of viscosity on a wide range of shear rates of whole blood from healthy human subjects were reported in 1968 at our last Congress in Kyoto [3] and in 1970 [18]. Hematocrits were 47.5 and 30 per cent, and the measurements below 10^{-2} sec^{-1} showed a downward slope in one of the curves plotting $\dot{\gamma}$ against τ . Since these findings were reported, many more measurements have been made, which, however, did not always exhibit the same downward slope.

In our measurements on the viscosity of whole blood from healthy human donors, we used the Weissenberg Rheogoniometer, which was modified for biorheological studies [33]. We employed a combined Couette and cone plate geometry similar to that originated by MOONEY and EWART [34].

In Fig. 1, a diagrammatic view of the geometry used for these measurements is shown.

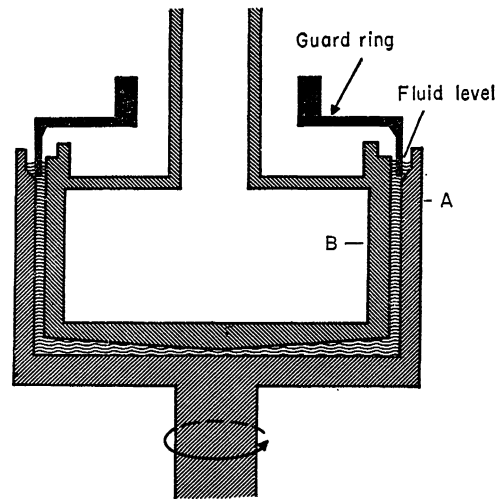


FIG. 1. PLAN VIEW OF GEOMETRY SHOWING POSITION OF REMOVABLE GUARD-RING.

The unit was made in two sizes: one size had a radial gap of 0.75 mm with a 1° conical end, while the second one had a radial gap of 3.0 mm and a 4° conical end. The vertical gap size was selected so that the shear rate in the Couette region would be the same as that in the conical region. The measuring elements were made of Plexiglass which had been siliconized.

The blood was drawn from the antecubital vein of healthy human donors, ranging in age from 25 to 60 years. The blood was mixed immediately with dry ethylenediamine tetraacetate, EDTA (1.2 mg/ml), as an anticoagulant, thereby eliminating blood dilution.

Measurements were made both in the presence and absence of the detachable guard-ring which is used to eliminate the torque which may be developed by surface layers of plasma proteins. We found no differences in the results with or without the use of the guard-ring, as can be seen in Fig. 2. The light circles in this Figure indicate data obtained without the guard-ring, and the dark circles represent the findings secured with the guard-ring.

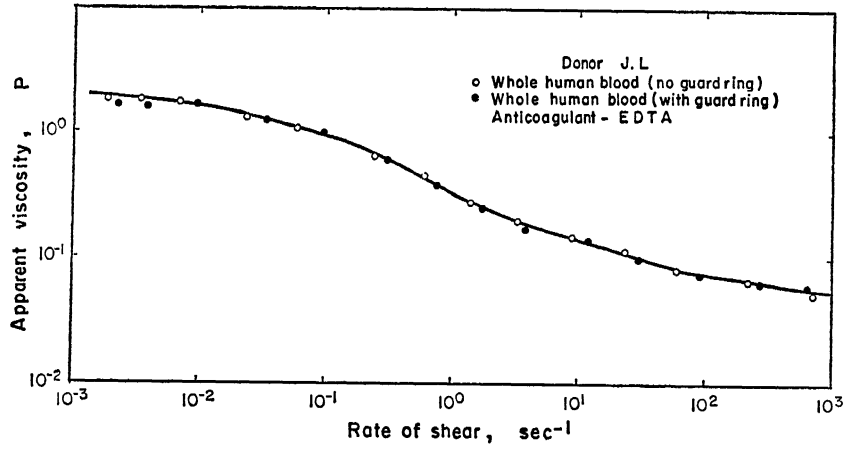


FIG. 2.

The following equation of state for thixotropic fluid, in Freundlich's sense, developed by HUANG [35] was proposed [19] to characterize flow properties of blood:

$$\tau^{ij} \pm \tau_0^{ij} = - \left[\mu \pm C_1 \xi \beta_{(exp)}^{ij} \frac{|\dot{\gamma}^{ij}|^n}{\dot{\gamma}^{ij}} e - C_1 \int_0^t |\dot{\gamma}^{ij}| dt \right] \dot{\gamma}^{ij} \text{ if } \tau^{ij} > \tau_0^{ij}$$

where τ^{ij} is the shear stress tensor; $\dot{\gamma}^{ij}$, the shear rate tensor; τ_0^{ij} , the yield stress tensor; $\beta_{(exp)}^{ij}$, the equilibrium molecular arrangement parameter of erythrocytes; t , the time; μ , C_1 and ξ are constants. In the equation given, the superior symbols do not indicate contravariance.

In Fig. 3 three representative flow curves are shown from the data secured from the blood of 80 healthy human male and female donors with red blood cell volumes, or so-called hematocrits, ranging from 30 to 50 per cent. The shear rate scale was divided into three regions: Region I from 50 to 1000 sec^{-1} , Region II from 0.01 to 50 sec^{-1} and Region III from 0.001 to 0.01 sec^{-1} .

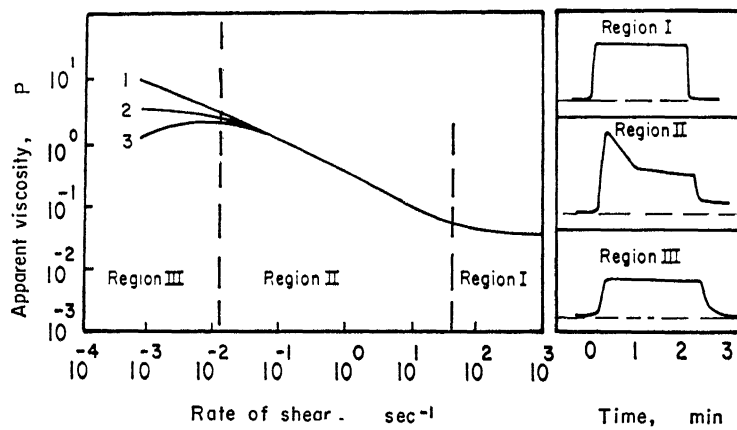


FIG. 3.

In Region I ($50\text{--}1000\text{ sec}^{-1}$), the blood behaves mainly as a Newtonian fluid. In this region, it is assumed that the aggregating force, which causes the formation of rouleaux, is much less than the desaggregating shear force, which breaks any rouleaux which may have formed into individual red blood cells. Only single red cells exist above a shear rate of approximately 50 sec^{-1} [36]. Therefore, above this rate of shear the blood behaves as a homogeneous Newtonian fluid. From the flow curve, predicted from the equation shown above, the shear stress is proportional to the shear rate at high shear rates. A typical example of a recorder trace measured in this region is shown on the right-hand side of Fig. 3.

In Region II ($10^{-2}\text{--}50\text{ sec}^{-1}$), the blood viscosity depends on the rate of shear and also on the time of shearing. Such a fluid is considered to be thixotropic according to phenomenological macrorheology. A typical recorder trace for this region is shown on the right-hand side of Fig. 3. The thixotropic behavior of blood in this shear rate range probably arises from the progressive break-down of rouleaux under shear. In addition, erythrocyte sedimentation and possible migration of proteins and erythrocytes at the interface of blood and the wall of the viscometer may play a role in the measurements of the rheological behavior of the blood. Therefore, the validity of reported findings is open to doubt. It is of interest that only in the recorder trace of Region II, obtained after the cessation of shearing, the recovery curve fails to return to zero, suggesting that blood has a yield stress.

At constant shear rate, the torque-time curve reveals a decay of the torque after it reaches a peak value in this region. In view of the above mentioned possibility of artefacts in measurements of the rheological behavior of blood, the peak value of the torque is used for the calculation of the shear stress. Our findings demonstrate that all blood samples exhibit a decrease in apparent viscosity with increasing shear rates. This rheological behavior, as well as the torque decay, can be represented by the above equation. It should be noted that the equation covers not only the time-dependent behavior of blood, but also the wide range of shear rates from 0.01 to 1000 sec^{-1} . The CASSON equation [37] has been extensively used for blood systems, ever since it was first applied to them by SCOTT BLAIR and COPLEY [38-43]. This equation does not predict the time-dependent behavior of blood and is applicable only over a limited range of shear rates.

DINTENFASS [30] has reported findings which differ markedly from ours in Region II and those by CHIEN *et al.* [28]. Dintenfass reported measurements of viscosity of blood with samples obtained from 10 healthy human subjects. He tested the samples immediately

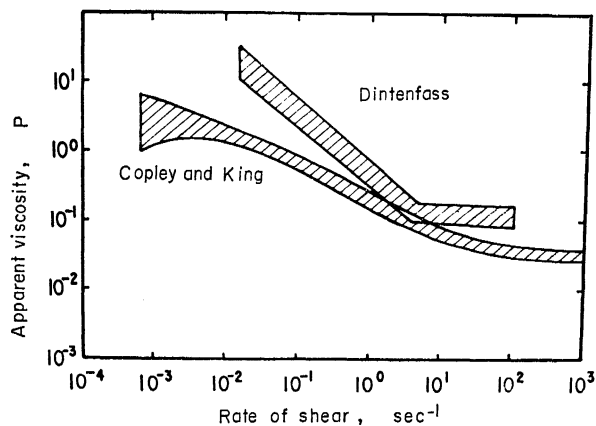


FIG. 4.

after withdrawal without the use of anticoagulants, employing a cone in cone viscometer with shear rates down to nearly 0.01 sec^{-1} . His findings are compared with our findings in Fig. 4.

It can be seen that our findings differ widely from those DINTENFASS [30] reported at the shear rates he could employ with his instrument. The only explanation we can offer for this marked discrepancy, which is of the order of up to 10-fold at the lower shear rates, is that fibrin formation and polymerization might well have begun in the blood samples, tested by Dintenfass, since no anticoagulants were used in his study.

It is known that the coagulation process, i.e. the conversion of fibrinogen to fibrin, commences as soon as blood has been shed, subsequent to the activation of thrombin. In light scattering studies of fibrinogen-thrombin systems COPLEY *et al.* [3, 44, 45] demonstrated the rapidity with which fibrin polymerization occurs.

No discrepancy, however, exists between our findings and those of CHIEN *et al.* [28]. These authors used the GDM viscometer which has a Couette-like geometry. They used non-diluted blood, anticoagulated with heparin. Their measurements were made at varying shear rates down to 0.01 sec^{-1} . As their geometry differed from the one we used, the different type of geometry cannot be made responsible for the large discrepancy between our findings and those of Dintenfass.

In Region III (from 0.001 to 0.01 sec^{-1}), we found three typical types of behavior, as is shown in Fig. 3. In the first curve, the viscosity increased steadily with decreasing rate of shear. In the second curve, the viscosity approaches a constant value, while in the third curve the viscosity appears to decrease. A typical recorder trace of measurements in this region is shown on the right-hand side of Fig. 3.

In the 80 samples measured, these characteristic curves were numerically about equally distributed. Slopes 1 and 3 may be due to a scatter because of instrument difficulties at the high sensitivity employed during these measurements. Therefore slope 2 may well represent the actual rheological characteristics of whole blood in Region III. At present, no quantitative explanation for these differences in the slope can be offered. It is proposed that the blood flows like a solid plug in this region of minimal shear rates. We postulate that the associated shear stresses in Region III are less than the yield stress of blood, and that then rouleaux of red blood cells will continue to exist, which will cause the structure to flow as a plug. Slip may occur at the blood-wall boundary on a plasma layer. Two factors will contribute to the maintenance of a stable, solid plug of blood, namely (1) the van der Waals forces [46] of attraction between erythrocytes and (2) the forces of physical and/or chemical links at points along the chains [47] of the rouleaux arising from polymeric bridging.

The shear modulus of blood, having the characteristics of a solid below the yield value, which will be a function of its chemical, physical and electrical interactions as well as of its surface properties, is poorly understood. Therefore, an indirect effect such as the shear strain on the shear modulus, which is expected to alter these properties by imposing an extra force field, has, to our knowledge, hitherto not been previously described. In this region of minimal shear rates our results show that the shear modulus of blood, which behaves as a solid, may be increased, decreased or unaltered by the increase of the shear strain.

It can also be seen from Fig. 3 that, at a shear rate of about 0.01 sec^{-1} , there is a change in the slope of the curve. We suggest that this may be the point where the column of red blood cells, which flows as a plug, breaks down, and a transition to laminar flow begins. This may well be the manifestation of the actual yield point. Therefore, the shear stress at

this point might be the real measure of the yield value, in contrast to an estimate based on the generally employed extrapolation technique using Casson plots.

In our earlier communication in 1970 [18], we referred to the need for using different gap widths and cone angles in order to establish the effect that they may have on the flow properties of whole human blood. At that time we used different gap widths and cone angles in our studies, but our findings could not be obtained with blood samples from the same blood withdrawal, and, therefore, they could not be conclusive. Recently, we could study this problem again, when two Weissenberg Rheogoniometers could be used in the same laboratory. Thus, we were able to examine the flow properties of identical blood samples simultaneously in two Weissenberg instruments. The radial gap sizes were 0.75 mm with 1° cone angle in instrument A, and 3.0 mm with a 4° cone angle in instrument B.

Our findings with the blood of one donor are shown in Fig. 5. A further comparison was made by drawing the blood from the same donor again after an interval of 3 days, and making comparative studies employing the two different gaps. The curves with the crosses correspond to the 0.75 mm gap and the 1° conical end, and the curves with the circles correspond to the 3.0 mm gap and the 4° conical end. In the upper and lower two curves no significant change occurred at shear rates down to 10^{-1} sec^{-1} . The results secured by the instrument with the smaller gap show a curve which tends to come to a plateau. The lower two curves, exhibiting data with the blood drawn from the same subject 3 days later, show a remarkable duplication of the results obtained with the two gaps. In a theoretical study, GAZLEY confirmed to some extent our findings with the different gap sizes [48].

At low rates of shear, below 10^{-1} sec^{-1} , results obtained with the small gap show a levelling off, while those secured with the larger gap exhibit higher viscosities. The hematocrit

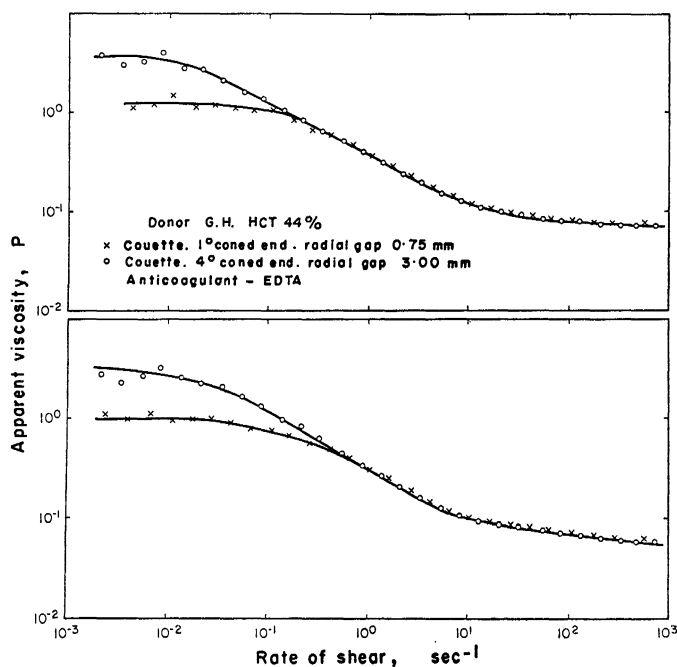


FIG. 5.

of the two blood samples remained constant at 44 per cent. Similar findings were obtained with the blood secured on different days from another healthy human subject.

Our data are of particular interest for Region III of minimal shear rates. It is generally accepted that blood has a yield stress [2, 4, 49]. In such a case, the viscosity values should be infinitely high in this minimal shear rate region. As this does not occur with our measurements, plug flow must be occurring with slip at the geometry interface. In the case of plug flow, our viscosity values may not be meaningful as measures of the viscosity of whole blood.

Our findings, however, in Regions I and II characterize the flow properties of whole blood from 1000 down to 10^{-2} sec^{-1} , for which we have presented an equation of state and also other pertinent explanations which we consider valid.

I shall now deal with the other area of my studies in recent years. It is related to the main killer in the Western world, namely thrombosis, which can be considered a truly hemorheological disease.

Concepts of the initiation of thrombosis, first proposed more than a century ago, have been based on two major hemorheological processes of *in vivo* blood clotting, found to occur either separately or mixed, viz. the clumping of blood cellular elements and the coagulation of plasma by the formation of fibrin from its precursor fibrinogen. Thrombus formation was considered to be intravascular clotting in any of the forms mentioned, or combined, resulting in partial or complete obstruction of blood vessel segments and leading to impairment of the circulation. To these two concepts I advanced last year a third one, unknown before [21–23].

This concept is based on the formation of polymolecular layers of fibrinogen and other plasma proteins leading to obstruction of the affected blood vessels. This aggregation of proteins is considered to occur in two steps. A first adsorption process would occur on the surface of the endothelium, facing the lumen of the blood vessel. This first adsorption step appears to be favored by the physiological occurrence of the different forms of fibrin, the so-called cement fibrin, which I proposed first in 1953 as the endoendothelial fibrin layer to cover the endothelial cells [50]. Since fibrinogen and other plasma proteins were found to have a great affinity to fibrin, this first adsorption process would be facilitated. This first step is followed by a growth process, in which additional protein molecules adsorb on previously formed adsorption layers in the lumen of the affected blood vessels.

This deposition of plasma proteins in layer upon layer on the inner lining of the vessel wall would constitute the initial thrombus. It would then grow contiguously and, subsequently, affect large blood vessels, a process followed by fibrin formation, polymerization, gelation and/or blood cellular clumping.

This concept promises to initiate entirely new approaches in detecting a susceptibility towards the development of thrombotic conditions in the blood of apparently healthy human subjects, and in the prevention, diagnosis and treatment of thrombosis.

According to this concept a marked increase in the non-homogeneous distribution of fibrinogen and other proteins in solution would lead to their proposed deposition. By non-homogeneous distribution is meant the time-dependent, progressive adsorption of the plasma proteins from the solution at the interfaces with the vessel wall and the free surface of the adsorbed proteins.

Such a possibility may be related to considerations of COPLEY and STAPLE [51], made 10 years ago, as to whether a suspension of macromolecules would show a radial distribution when flowing through a capillary tube in which the velocity gradient from the axis to the wall of the tube was steep.

Last April, a paper on electrical field-flow fractionation of proteins by CALDWELL *et al.* was published in the journal *Science* which appears to support our earlier considerations [52]. Field-flow fractionation, proposed by GIDDINGS in 1966 [53, 54], is a separation method in which various applied fields, working in conjunction with cross-sectional flow nonuniformities in a narrow tube, cause the differential migration of molecules and ions. There may well be a higher transport rate for larger molecules than for smaller ones. It appears that their findings would substantiate our contention of a nonuniform distribution of particles across a flow channel. Further studies on the distribution of protein molecules in flowing blood in capillary tubes and in living blood vessels are needed.

EIRICH [55] referred to the profound surface effect of the macromolecules including polyelectrolytes in many types of interaction involving macromolecules. Our earlier *in vivo* hemorheological observations on the more or less immobile layers next to the endothelium, first proposed by POISEUILLE in 1839 [56], and the phenomenon of wall adherence, described by COPLEY and SCOTT BLAIR [39-41, 57], may also have a bearing on the formation of polymolecular layers of fibrinogen and other plasma proteins in flowing blood.

In our viscous resistance studies we followed in principle the approach of JOLY [58, 59], who, in some of his studies on surface viscosity, measured the viscosity with a Couette geometry with and without a guard-ring.

We define "viscous resistance" or "overall viscosity" as a value calculated from an average of the torque derived from the bulk of the test fluid plus that of its polymolecular surface layers. We prefer the use of the term "viscous resistance" [24], as, to my knowledge, it has not been used specifically. In some of our earlier publications, however, we used the term "overall viscosity". Accordingly, our findings were plotted as apparent viscosity vs rate of shear and we referred to the curves as viscosity profiles. Although it was always made clear that overall viscosity was meant, we now prefer to present our findings more directly as torque, τ , vs rate of shear.

We used the Weissenberg Rheogoniometer, with the modifications we made for hemorheological studies [33]. The apparent viscosity was measured at shear rates from 1000 to less than 0.1 sec^{-1} . In the combined Couette and cone and plate system used, a geometry similar to that described by MOONEY and EWART [34], surface layers form at the interfaces of the test sample of plasma protein solution and the surfaces with which it comes into contact. These surface layers contribute added torque to the measuring inner platen which is particularly marked at low shear rates. A stationary guard-ring, attached to the main body of the rheogoniometer, is used, as shown diagrammatically in Fig. 1. The guard-ring is entirely detached from the driven, rotating outer platen and the measuring inner platen. This guard-ring excludes transmission of the torque from the surface layer to the measuring platen.

Several investigators [28, 60, 61] reported findings that plasma systems and fibrinogen solutions exhibit non-Newtonian behavior, if the precaution of using a guard-ring is not applied. However, these investigators did not consider their findings, obtained without a guard-ring, as a phenomenon in need of further study, but rather as an artefact to be avoided.

Viscous resistance is always measured without the guard-ring. In Fig. 6 the viscous resistance of a 0.4 per cent fibrinogen solution is compared to that of physiologic saline (0.9 per cent NaCl). As expected, the plot exhibits Newtonian behavior of the saline, but marked non-Newtonian behavior of the fibrinogen solution.

Figure 7 shows a plot of five experiments of the same 0.4 per cent fibrinogen solution,

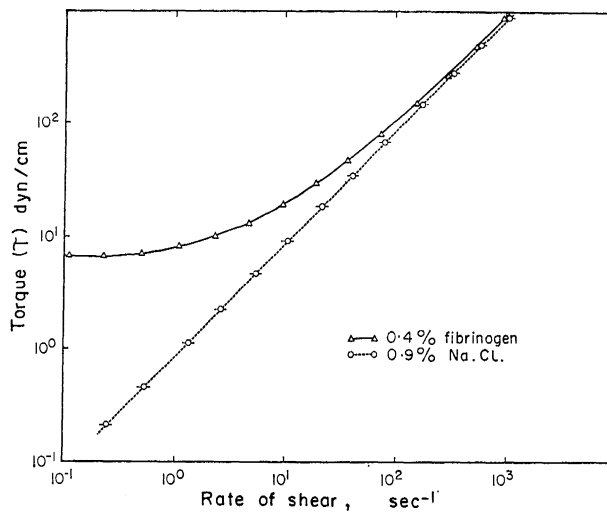


FIG. 6.

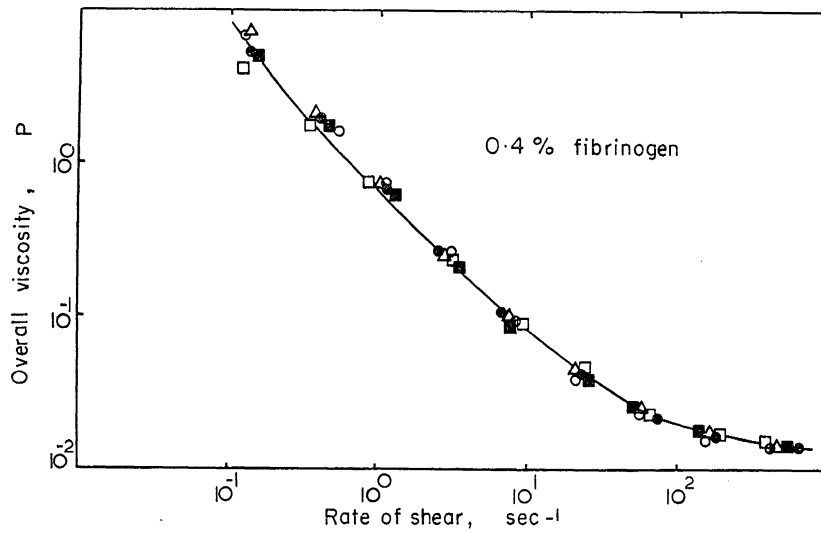


FIG. 7.

measured separately without a guard-ring on the same day. These findings demonstrate that the overall viscosity or viscous resistance of the surface layers of fibrinogen is consistent.

A comparison of torque values of two fibrinogen concentrations, obtained with and without the guard-ring, is shown in Fig. 8. The curve obtained when using the guard-ring, which eliminates measurements of surface layers, shows Newtonian flow characteristics. As expected, the higher fibrinogen concentration (dark triangles) results in a higher torque, indicating a higher viscosity. Without the use of a guard-ring a marked increase in τ values occurs below the shear rate of 10 sec^{-1} . This indicates that apparently thicker and stronger surface layers of fibrinogen form with the higher fibrinogen concentration at the test fluid-air interface of the viscometer geometry.

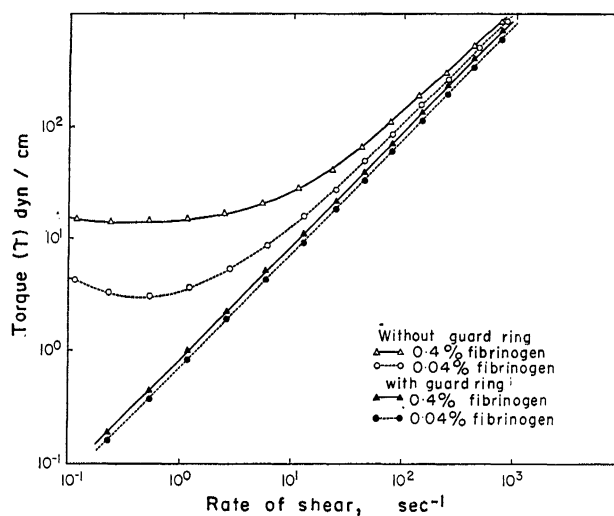


FIG. 8.

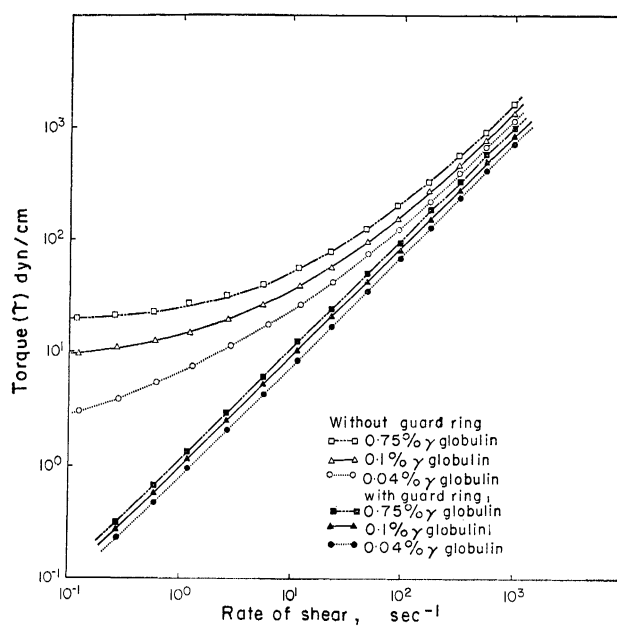


FIG. 9.

Similar results have been secured with solutions of gamma globulin, as can be seen from Fig. 9. Here the dark circles, triangles and squares mark viscosity values, secured with the guard-ring, of concentrations of 0.04, 0.1 and 0.75 per cent gamma globulin, while the corresponding light markings refer to values, secured without the guard-ring. As can be seen, viscous resistance is markedly increased with higher gamma globulin concentrations, particularly below 10 sec^{-1} .

In Fig. 10 plots of τ of albumin solutions are presented. They are derived from the surface layers only, and obtained by subtracting the torque, derived from the bulk solution

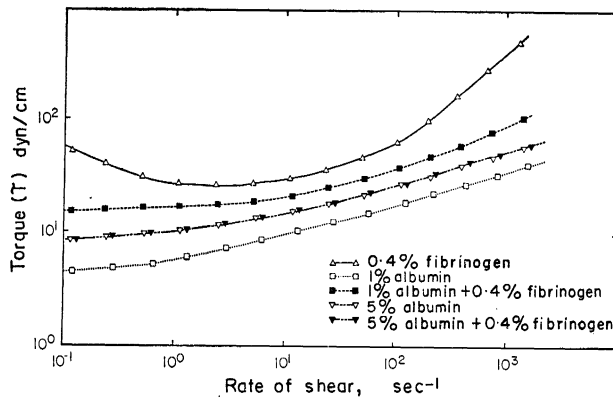


FIG. 10.

with the guard-ring in place, from the torque measured without the guard-ring. Torque values of concentrations of 1 and 5 per cent albumin with and without the addition of 0.4 per cent fibrinogen and fibrinogen as control are compared. Although the concentration of fibrinogen (light triangles) is much lower than that of the 1 per cent albumin (squares) and of the 5 per cent albumin (inverted triangles), the albumin preparations give much lower τ values. However, when the same fibrinogen concentration is added to both albumin solutions, the comparison shows no difference with the 5 per cent albumin, but an increase in τ with the fibrinogen—1 per cent albumin (dark squares). It is noted that these values are much lower than those of the fibrinogen control (light triangles). Since albumin is generally considered to be one of the main protective colloids, it may act in reducing the successive adsorption of monomolecular layers of fibrinogen at the boundary.

Figure 11 shows a comparison of viscous resistance of surface layers of 5 and 18 per cent serum with and without added 0.4 per cent fibrinogen, and with 0.4 per cent fibrinogen as control. Very low τ values were obtained with the 5 per cent serum (lowest curve). If fibrinogen is added, the values are markedly increased (second curve from above) and approach the fibrinogen control (upper curve). However, the τ values with 18 per cent serum with and without fibrinogen do not exhibit any change. These findings indicate the

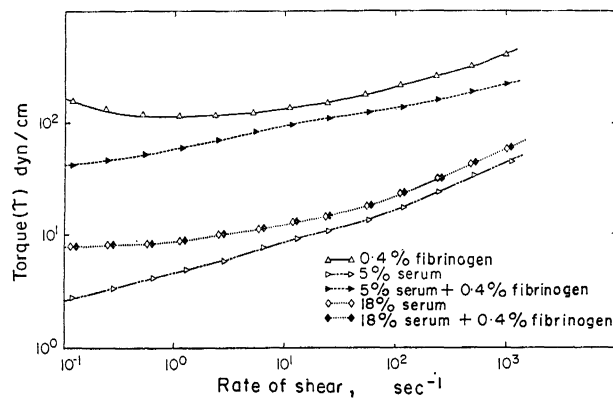


FIG. 11.

presence of a critical concentration of serum, when the addition of the same amount of fibrinogen will not cause any increase in values. Similar findings were shown with plasma. Both the plasma and serum may also contain protective colloids other than albumin which have a similar action on fibrinogen.

We obtained a number of other interesting findings which time will not permit me to present. Of special interest are our new results with regard to the action of red blood cells and platelets on viscous resistance of plasma protein systems which we are going to report here at the Congress of Biorheology [25].

KING and I also made preliminary observations on the viscoelasticity of surface layers of a 0.4 per cent fibrinogen solution. The method which we employed is described by us in an exhibit at our Congress [26].

Our findings show the definite presence of an elastic component as you will note from Fig. 12. The phase difference between the two traces is 28° . As is generally known, the phase difference would be 90° in a material exhibiting Newtonian behavior.

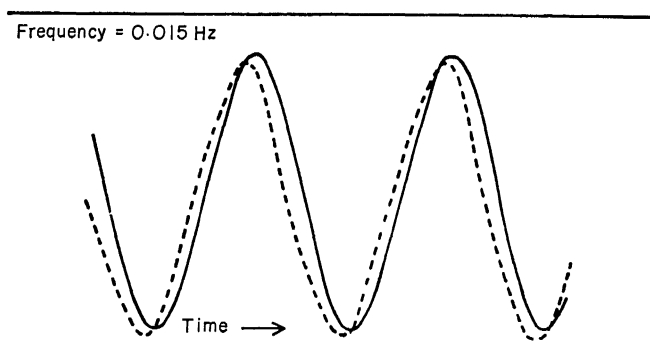


FIG. 12. THE INPUT MOTION TRACE (SOLID LINE) AND THE OUTPUT TORQUE TRACE (DOTTED LINE) OF A 0.4 PER CENT FIBRINOGEN SOLUTION, USING THE OSCILLATORY MODE OF THE WEISSENBERG RHEOGONIOMETER. The phase difference is 28° .

Work is in progress with regard to comparative studies of viscoelasticity, viscous resistance and the composition of the surface layers of different systems of plasma proteins. These new studies are being made jointly with Professors Israel Miller and Alex Silberberg of the Weizmann Institute of Science. These joint studies in both our laboratories in Rehovot and in New York City were initiated by my good friend, the late AHARON KATCHALSKY [62].

I am now coming to that part of this lecture which deals with biorheology as it is practiced as an art in medicine and surgery.

Descriptions of biorheological phenomena go back into antiquity [63–65]. Hippocrates, the ancient Greek physician (*ca.* 460–*ca.* 370 B.C.), who placed medicine on a scientific basis through systematic observation of disease, was aware of biorheological phenomena [66]. In the writings which have come down to us under the name Hippocrates, I should like to cite some phenomena which he described. He correlated the thickness of discharges and of other body fluids and the change in their consistency with a number of diseases. In his treatise “On Ancient Medicine” he says “And it appears to me that one ought also to know what diseases arise in man from the powers and what from the structures. What do I mean by this? By powers, I mean intense and strong juices; and by structures, whatever conformations there are in man.”

Hippocrates talks about the hardness of organs, their density, sponginess and “loose texture” such as the spleen and lungs. He said: “Those parts which are hollow and expanded are most likely to receive any humidity flowing into them, but cannot attract it in like manner. Those parts, which are solid and round, could not attract a humidity, nor receive it when it flows to them, for it would glide past, and find no place of rest on them. But spongy and rare parts, such as the spleen, the lungs and the breasts, drink up especially the juices around them, and become hardened and enlarged by the accession of juices. Such things happen to these organs especially.” He gives many other examples of biorheological phenomena.

The approach of Hippocrates of manually testing the consistency of organs in patients continues to be, in our time, a main tool of the physician and surgeon whom the patient consults. In some diseases such as, for instance, ovarian cancer, it unfortunately remains today thus far the only tool which leads to the discovery of the disease. For gross examination of anyone of us, this art of subjective or psychorheological testing by the hands of the physician represents practical biorheology as it is practiced daily in medicine and surgery. Thus, every physician and surgeon practices biorheology without being aware of it. I doubt that this art will ever be entirely replaced by instrumental techniques providing quantitative measurements, although this is already done by the ophthalmologist using the tonometer.

In my Inaugural Address before our two Congresses this morning held in this festive Palais des Congrès in Lyon, I gave a brief survey of biorheology as an organized science [1]. I believe, I should end this lecture in giving some examples of scientific thought in the history of science. These thoughts and great discoveries emphasize the present need of the biological sciences toward their advancement by the new physical science of rheology. This has been historically a rather slow process which culminated in 1948 at the First International Congress on Rheology [67] in the emergence of the science of biorheology [1, 67, 68].

The contribution of HARVEY (1578–1657) “*Exercitatio anatomica de motu cordis et sanguinis in animalibus*” (An Anatomical Disquisition on the Motion of the Heart and Blood in Animals”) [69, 70] rendered GALEN’S doctrine [71, 72] on the flow of blood (“On the Functions of Parts of the Human Body”) obsolete, which ruled medicine since the second century A.D.

Giovanni Borelli (1608–1679), a student of Galileo Galilei, published in 1667 “*De vi percussione liber*” and in 1670 “*De motionibus naturalibus a gravitate pendentibus*”. These two books deal with problems of mechanics and impulsive motion. They were an introduction for the better understanding of his theory of animal motion. In “*De motu animalium*” which appeared 1 year after his death, and was also published here in Lyon about 5 years later in 1685, BORELLI [73] dealt with different aspects of motion. “Motion” was not merely meant to mean external local movement but as well the internal movement of fluids and particles which comprise the living organism. It was Borelli who, in this book “On the Motion of Animals”, was probably the first to think of chemical processes behind the mechanical activity of muscular contraction.

Borelli’s pupil MALPIGHI (1628–1694) discovered the blood capillaries. In his classical experiment [74] he tied the lungs of a frog and watched with a microscope the flow of blood in the lung’s capillaries. However, it was LEEUWENHOEK (1632–1723), this most remarkable self-trained biologist, who demonstrated the living circulation in the network of the blood capillaries (or, as it is now called, microcirculation) with the aid of his home-made microscope [75, 76]. Leeuwenhoek thus provided the experimental evidence that

Harvey postulated in his theory, which became one of the principal events in the history of science.

Studies of flow properties of living matter thus began with the discoveries of Harvey, Malpighi and Leeuwenhoek pertaining to the circulation of blood, as well as later, in 1774, with the discovery of the streaming in plant cells by CORTI [77, 78].

POISEUILLE first reported in 1835 [79] his *in vivo* studies “Recherches sur les causes du mouvement du sang dans les vaisseaux capillaires”, which led to the application of rheological treatments to the flow of blood [56, 80]. The discovery of the laws of flow was based on experiments which Poiseuille was stimulated to make from his observations in living blood capillaries, resulting in his studies “Recherches expérimentales sur le mouvement des liquides dans les tubes de très petits diamètres” [80, 81]. These reports, published from 1840 to 1842, were accepted throughout Europe. On the basis of Poiseuille’s findings, Maxwell, Jacobson, Mathieu and others deduced from the fundamental equation of Newton the well known formula for viscosity, which was later named after POISEUILLE and HAGEN [81].

There are other reciprocal stimuli from biology and rheology, which promise to continue to be fruitful. Numerous biological phenomena and processes await a rheological approach for the characterization of the flow properties involved and for quantitative studies.

The development of our planet consisted in the past, as presumably it will consist in the future, of series of rheological occurrences. So does the development of life from its far distant past to its far distant future. Thus, biorheology is a science which encompasses all forms of life of all times on this planet. And as the earth appears to be ruled by universal laws of nature, in which rheologically REINER’s Deborah number [82] may play a role, so is the biorheological approach to problems of life and to those of our human existence. So, biorheology is significant in connecting on many levels the biological sciences with rheology.

HERMANN VON HELMHOLTZ (1821–1894), who made manifold studies in physiology and physics, was fascinated by the problem of the existence or non-existence of the so-called “vital force” belonging only to the living organism. His basic premise was always the “comprehensibility of nature”. In his lecture “On Human Vision” (Ueber das Sehen von Menschen”) in 1857 [83] he conceded to philosophy the undisputed right to investigate the sources of our knowledge. He thought that no age may evade the investigation of these sources. Earlier, in 1847, in his lecture “Conservation of Energy” [84] he says: “In the end the goal of the theoretical sciences is to discover the final, invariable causes of natural processes.” He has no answer to the question “whether nature must be entirely comprehensible or if there are alternatives in her which deprive the laws of a certain causality and thus allow the laws spontaneity or freedom”. In his lecture “On the Interaction of Natural Forces”, delivered in 1854 [83], Helmholtz said: “Physico–mechanical laws are, as it were, the telescope of our spiritual eye, which can penetrate into the deepest night of time, past and to come”.

About 2400 years ago, Heraclitus said: “It is not possible to step twice into the same river” [85, 86]. Ever since, philosophers have paid little attention to the idea of flow.

Among the philosophers of this century, it was Henri Bergson who has made the idea of flow an essential part of his thinking. I should like to conclude by citing one sentence from “L’Evolution Créatrice” (“Creative Evolution”): “The flux of time is the reality itself, and the things which we study are the things which flow” [87]. “Le flux du temps devient ici la réalité même, et, ce qu’on étudie, ce sont les choses qui s’écoulent” [88].

Thank you very much!

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