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FAHRAEUS AWARD LECTURE

THE IMPORTANCE OF RHEOLOGICAL THEORY IN CLINICAL HEMORHEOLOGY

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1. INTRODUCTION

Until very recently, blood rheology was seldom mentioned in most of the books dealing with physiology or physiopathology (1). However, it has been shown that the understanding of blood flow, particularly in the microcirculation, is closely connected with the rheological properties of blood and its components (2,3). The ever more detailed explanation of pathological phenomena needs parallel progresses in theoretical knowledge. This approach can only be attempted if "new theoretical concepts" are elaborated, taking into account the major variables and moving continuously back and forth between theory and clinical reality (4,5,6).

It is extremely difficult to describe the present state of research in clinical hemorheology, its vitality and the promises it holds for the future. Indeed, from the point of view of the fundamentalist, one may ask how is it possible to achieve any progress in a science where nothing is static as everything is deformable, where nothing is permanent as everything evolves ! How then are we able to perceive what is essential and how reliable is a science where measurements are often open to question ? However, the medical sciences have been capable of providing theories to explain and measure abnormal occurrences in the fundamental processes. Hemorheology has developed over the past twenty years as a result of research regarding fundamental processes. Research made in this field has led to a greater awareness in the manifestations of pathological phenomena. Equally, the problems arising from the physiology of blood circulation and exchange processes undoubtedly supply the rheologist with ample opportunity in becoming acquainted with these problems. Such an exercise is not an easy one, as the solid mechanics involved refers to rather limp, complex-structured media and the fluid mechanics refers to heterogeneous fluids. In spite of these differences, hemorheology should be considered as an integral part of rheology. If it can be said that hemorheology is advanced by rheology, hemorheology brings equally its own

contribution to fundamental rheology. Because of the original nature of the problems involved, hemorheology could therefore act as a stimulant for rheology.

In order to understand physiological flow and associated pathological symptoms, there is a need to lay the foundations for a new type of rheology aimed at studying media and conditions that are infinitely more complex than those generally studied in conventional rheology. At the same time, physiologists, biologists and clinicians, must give great care in defining their observations and measurements.

In this lecture I shall attempt to illustrate these various points with the help of some examples.

2. NECESSITY OF MODELS IN HEMORHEOLOGY

"Everything should be made as simple as possible but no simpler"
A. Einstein

The primary function of blood circulation is to transport oxygen and vital molecules for cell metabolism to the tissues and to carry carbon dioxide and waste matters to the organs responsible for their removal from the body.

For a better understanding of the mechanisms involved, one of the aims of hemorheology is the analysis of direct or indirect effects of various parameters on blood flow. Viewed from a mechanical aspect, blood flow can be diagrammatically divided into three major classes according to the values of the ratio α of blood vessel diameter 2R to red cell dimension 2a (7).

a) capillary circulation ($\alpha \leq 1$), where very high red cell deformation occurs, and which is consequently governed by the red cell's rheological properties, i.e. membrane visco-elasticity and the viscosity of the cell's internal fluid ;

b) systemic circulation ($\alpha > 50$) in the arteries and veins, where high deformation of the vascular wall, accompanies pulsed flow in the arteries. At this level, blood flow will therefore mainly depend on the rheological properties of the blood and vessel walls ;

c) microcirculation ($1 < \alpha < 50$) in the arterioles and venules where the so-called "anomalous" properties of blood are observed (i.e. primarily blood's non-Newtonian properties) connected with a fundamental characteristic of blood flow at this level, namely the formation of a peripheral plasma layer, free from red cells, which are all concentrated in the axial region of the blood vessel. The existence of this type of two-phase blood flow results in oblate velocity profiles and special effects such as the well-known Fahraeus-Lindqvist and Fahraeus effects.

For the interpretation of these different types of blood flow, knowledge regarding the rheological properties of blood must be available. Hemorheology sets apparently almost inextricable problems for rheologists. It requires setting the foundations of theory that remains valid at the microscopic scale for a heterogeneous medium with compositions and structures that are apt to change with time and with components whose physical constants depend on their state of motion. We are therefore faced with an open system in the thermodynamic sense of the term. Up until now, though, theoretical rheology has made very little progress in this direction.

It can, however, be hoped that an adequate choice of models, based on experimental facts, will provide the means of theoretical approaches to understand the phenomena observed and at the same time improve fundamental rheology.

As in every field of physics, there are two major categories of models that can be applied in hemorheology :

. Descriptive models that take into account the laws of physics which apply to blood and the blood components,

. Mathematical models that disregard the subjacent elementary mechanisms and put forward presumptive equations which will have to be compared with the experimental data.

The descriptive models are obviously more satisfactory as they take into account the physical properties of the different parts of the system. In contrast, these models require comprehensive knowledge of the laws which apply to blood and the blood components. In fact, in a system as complex as blood, the actual facts are much less clear-cut and intermediate rheological laws have been developed up to now. For this reason that there is no unity in the models proposed.

At present, a theoretical approach appears to be practically impossible, as the system examined is a non-uniform suspension, made up of visco-elastic and non spherical particles (red blood cells), that form a heterogeneous system, which is further complicated by particle aggregation. What is really required as a first step is a number of theoretical models that could be used during clinical trials for analyzing hyperviscosity syndromes. These models should be sufficiently complex to take into account the main parameters involved, yet at the same time not too complex so as to avoid introducing too many variables, which would make any interpretation quite illusory.

Casson's law is one of the first phenomenological relations which have been suggested. Experimental studies show that in normal blood this relation is satisfactory if $2 < \dot{\gamma} < 40 - 60\ sec^{-1}$, but at very low and high hematocrit values and at high and low $\dot{\gamma}$ values, this relation is no longer satisfactory. Furthermore, the yield shear stress τo cannot be measured directly using standard viscometric techniques. Certain authors have, however, been able to assess pathological changes in this parameter (i.e. in the case of diabetes, using a network of capillary tubes in vitro).

An interesting approach could also be anticipated, based on an extension of the concept of intrinsic viscosity and of the principle of optimum energy dissipation. Along these lines, Quemada has suggested extending a relation originally put forward for Newtonian fluids to include blood's non-Newtonian behaviour :

$$\eta_r = (1 - \tfrac{1}{2} K \varphi)^{-2}$$

In this case, intrinsic viscosity K being a structural parameter, is dependent on flow conditions. It is not easy to assess the true dependence of $K(\dot{\gamma})$, which is the outcome of various phenomena depending of the applied shear rate (desaggregation of the rouleaux network or of red cell aggregates, reduction in the size of rouleaux followed by their complete dissociation, red cell deformation and orientation). At a given $\dot{\gamma}$ value, dynamic equilibrium between these various processes is observed. In the case of blood, Quemada has suggested characterizing the structure at a given hematocrit value by applying a mean characteristic time τ and using the extreme intrinsic viscosity values $Ko = K(\varphi, o)$ and $K_\infty = K(\varphi, \infty)$ connected with the maximal states of

erythrocyte aggregation and deformation. A kinetic-type equation for describing the dynamic equilibrium "aggregation-disaggregation" will supply an equilibrium value (at a given $\dot{\gamma}$) that can be inserted into the ηr equation. In this case, the three parameters : Ko, $K\infty$ and τ, provide the means of partially characterizing the blood's rheological properties. Applying this model, we have carried measurements to assess the limits of the model with erythrocyte suspensions with different aggregation or cell rigidity states. In spite of highly satisfactory agreement between the model and the experimental data at $0.5 \prec \dot{\gamma} \prec 100\ sec^{-1}$, the values of K_o, $K\infty$ and τ no longer match and show where the limits lie with regard to the validity and sensitivity of this relation at extreme variations in microrheological parameters (RBC deformation or aggregation).

It is mere wishful thinking to expect that such simple characterization is all that is needed. Indeed, much research by trial and error and examination of numerous parameters will be required before it can be anticipated in choosing a specific model. However, we very quickly come up against the highly complicated nature of the calculations and some simplification is therefore needed.

Diagrammatically, partial problems involving a smaller number of parameters will have to be defined within the structure of the overall problem. This is the method applied, for example, when undertaking studies on blood's rheological behaviour during transient or oscillatory flows, where thixotropic and visco-elastic kinds of behaviour have been revealed. In order to discover the origin of these properties, particular attention will have to be given to examine the rheological properties of erythrocytes. Indeed, not only does the erythrocytes have rheological properties, but it also form a three-dimensional physiological (rouleaux) or pathological aggregate network with specific properties that are all important when investigating transient or periodic phenomena. The simplest and, at present, most widely used approach consists of submitting the fluid to a one-dimensional pulsed flow at frequency ω and studying the frequency response via the variations in complex viscosity η_c. Certain authors (Thurston) suggest using the η_c (ω) curves for interpreting the variations by introducing a behavioural law representing the parallel superposition of Maxwell bodies. The phenomenological approach attained with this method, however, is much too broad-based and provides no details on the real changes in structure. Therefore theories put forward for polymers in solution could most probably be extended to the rheological behaviour of blood. Carreau's theory, for example, which generalizes the concept of "temporary rupture in polymer bonds" could provide the means of progressing from the pure visco-elastic stage through to the stage combining both the visco-elastic and thixotropic effects generally observed in blood, taking into account changes in cell structure (4).

It may also be asked, why has hemorheology benefited so little up until now from the progress carried out in fundamental rheology ? Apart from the standard problems stemming from differences in terminology between the two sciences, the main reason for the lack of reciprocal research comes from the differences in the complexity of the systems studied.

Indeed, fundamental rheology is mainly concerned with investigating continuous and homogeneous - or at least elementary heterogeneous - media made up of components that are small compared with the size of the object measured. Furthermore, standard rheology is usually only concerned with studying solids with simple geometric shapes or fluids in simple shape measuring systems that are in most cases highly symmetrical. In the case of blood and blood flows, though, there are no such limiting factors. In particular, the "vessel-blood organ" (the concept and term introduced by A.L. Copley to emphasize the close

link between it two portions) forms an open system with variable limiting conditions. Moreover, in order to understand the phenomena involved, cellular scale structures (erythrocyte aggregation) and even molecular scale structures, such as erythrocyte rheological properties, must be taken into account.

Finally, it must be emphasized that in the case of blood flow, different scales of heterogeneity must be considered. Accordingly, the cells are macroscopic in comparison with the size of the plasma proteins, but the cell diameter is very similar to that of the capillaries, as it is microscopic when compared with the diameter of the large blood vessels.

All these factors provide an explanation for the weak contribution made by fundamental approaches to hemorheology and indicate that more specific theoretical models for reproducing the blood flow-cell structure relation must be constructed.

3. SOME HEMORHEOLOGICAL PROBLEMS THAT COULD BE OF INTEREST FOR THE FUNDAMENTALISTS

A large number of rheological phenomena observed at the cell scale play a fundamental part in shedding light on pathological phenomena. It is therefore of importance that research in theoretical rheology should support the numerous physio-pathological investigations that have been carried out over the past twenty years. I shall discuss some of the problems that could, in the long run, be solved with the development of new routine blood tests in the clinical laboratory.

3.1. Erythrocyte aggregation.

Erythrocyte aggregation is a highly important phenomenon in cellular biology, not only because of its influence on the rheological properties of blood, but also because it happens to be an easily accessible model for investigating the physics of cell-cell interactions in biological systems (8,9,10)

It was Fahraeus who first demonstrated that the physico-chemical properties and the concentration of the various plasma proteins played a part in erythrocyte aggregation. In healthy subjects, red blood cells form aggregates known as rouleaux ; but in many pathological states, the aggregates are much more complex structures, both morphologically and regarding their rheological properties. Aggregate size, geometry and cohesion all depend on different parameters, and in particular the bridging energy.

Aggregation with Dextran provides a relatively simple experimental model, but is still a long way from actual physio-pathological conditions. At present any attempt to generalize the results to include plasma proteins such as fibrinogen must take into account the specific nature of each protein. From a physico-chemical aspect, erythrocyte aggregation energy is produced by the formation of intercellular macromolecular bridges and disaggregation energy is the result of electrostatic repulsion between the adjacent cell surfaces when the cells move very close together. The observed repulsion energy proceeds essentially from the negative electrical charge found on the surface of the erythrocyte and, to a lesser degree, to the energy resulting from the change in R.B.C. membrane curvature during aggregation. When shear stress is present, the cells tend to disaggregate under the effect of the mechanical shear. Therefore, net aggregation energy between adjacent cells will depend on the balance of these 4 types of energy.

From a theoretical point of view, studies applied to simple dissociable, but non-deformable, spheric or ellipsoid aggregate models, or the stick-shaped aggregate models have not provided satisfactory approaches. It is most important that future theoretical investigations should take particular account of aggregate deformability and also of the fact that in the microcirculatory system the aggregated structures can never be larger than the diameter of the corresponding blood vessel. Moreover, in order to account for the part played by erythrocyte aggregates in pathological phenomena, it will also be necessary to take the kinetic aspects into account. Some investigations applying models have been undertaken to this effect within the framework of both reversible and non-reversible addition and condensation polymerization reactions. However, unlike normal polymer kinetics, these approaches take into account the geometry both of the sub-units and of the growing structure. The inclusion of loop formation reactions is shown to be crucial in obtaining physically realistic equilibrium solutions to the kinetic equations.

3.2. Relationship between erythrocyte rheological properties and molecular structure.

A large number of in-vitro and in-vivo experimental investigations have revealed red blood cell deformability and, in particular, the deformations sustained by the cells as they flow through the capillaries. Chien has supplied a qualitative definition of the part played by the erythrocyte rheological property on blood viscosity. But up to now, very few theoretical or modelization studies have been carried out. In order to approach blood's rheological properties and tissue exchange phenomena, knowledge regarding the erythrocyte's mechanical properties is essential. It is particularly of utmost importance that an approach to these properties be made by means of investigations based on cell geometry and on the molecular structure of the cell (2,4,11).

Passive deformation of the red blood cell under the effect of outside stresses is dependent on the structure of the cell protein cytoskeleton, as well as on lipid bilayer composition and structure and on the rheological properties of the internal hemoglobin solution . From a rheological viewpoint, it can now be assumed that the cytoskeleton plays a fundamental part in maintaining cell shape and in determining the elastic properties of the membrane. At present, however, an analysis of the published results reveals wide variations in assessments of this parameter. The scatter is only apparent though and can be attributed to the membrane's non-linear behaviour and to differences in the type of deformation involved. In fact three main types of elastic deformation can be described :

- deformation at constant area
- deformation with an increase in area
- deformation with changes in cell membrane curvature.

At present, the erythocyte membrane can be approached as a "solid-liquid" structure. The "solid structural" part is probably provided by the protein system. This network supplies the membrane with its resistance to extensional deformation at constant area and is responsible for the elastic reversibility of membrane extensions. The "liquid" component provides the resistance to any increase (or decrease) in membrane area.

For an accurate definition of all the aspects mentioned, fundamental rheological research on structurally anisotropic, organized fluids could undoubtedly provide improved awareness both of the cell's rheological properties and of the exchanges in which the cell is involved.

One of the consequences of the erythrocyte's rheological properties is the existence of a "tank tread-like rotation" of the membrane around the fluid cell content during shear deformation. This motion allows shear stresses to be transmitted to the cell interior and sets the cell into motion. The movement has been visualized experimentally in vitro by Fisher et al, who observed that the membrane tank tread motion is characterized by a single frequency at a given shear stress and is not influenced by the viscosity of the suspending medium. These results therefore reveal that the erythrocyte behaves differently from fluid droplets. Indeed, as concerns the latter, it is a well-known fact that the frequency of the interface motion is heavily dependent on the ratio of continuous phase viscosity to particle viscosity. Very little theoretical research has been undertaken for defining this phenomenon. Using a simple model and assuming the erythrocyte to be spherically shaped, we have shown that the "tank tread motion" appears as the result of solid body rotation caused by the flow superimposed at spatially constant deformation. Given the importance of tank tread motion in understanding oxygen and carbon dioxide transfer in capillary circulation, models somewhat closer to reality ought to be anticipated.

3.3. Blood flow in the small blood vessels (microcirculation).

Blood flow in the small blood vessels is characterized by (3,6) :

- the existence of a two-phased flow with the appearance of a cell-depleted marginal or plasmatic zone near the wall.
- a flattening of the velocity profiles in the vicinity of the axis,
- a decrease (during in vitro experiments) in the concentration of cells circulating in a capillary tube as compared with that in the reservoir (Fahraeus effect),
- a decrease in apparent viscosity (η_a) when the blood vessel radius decrease (Fähraeus-Lindqvist effect).

In contrast with other problems that occur in hemorheology, a considerable amount of research has been undertaken over the past twenty years on both "Fahraeus effects" and on the plasmatic zone, and the experimental findings have been thoroughly substantiated. Although theoretical approaches have been considered, it is a fact that the processes that initiate these phenomena are not as simple as they might appear. The theoretical aspect of the phenomena ought to be re-examined on a more general basis, in particular, in developing a more accurate definition of the significance of the phase separation induced by flow, and possibly taking into account the influence of shear rates on distribution functions.

Up to the present, studies have mainly been made on dual-phase models which always provide flattened velocity profiles, as the central phase is assumed to be more viscous than the peripheral phase. Although the models are satisfactory from a qualitative point of view, the results obtained are not usually quantitatively acceptable. Accordingly, in the case of the double-Newtonian model, the higher the ratio of the two viscosities, the flatter the velocity profile ; but in this case a rather crude ragged adjustment of the velocities is observed. The Newtonian-Casson model is more satisfactory. The yield shear stress values for the flattened part of the curve, as deduced

from the viscometric measurements, however, are very different from reality. The use of structural viscosity models such as those mentioned above could perhaps provide results somewhat closer to physiological reality.

3.4. Other problems.

There are a number of other problems that require new advances to be achieved in fundamental rheology. For example :

- Improved understanding of the detailed topography of the endothelial surface in term of relationships between local shear stress, enzyme activities, binding sites and intracellular material (8)
- Phenomena at the blood-vessel interfaces with, in particular, the "endoendothelial fibrinogenin lining (EEFL)", concept first introduced by Copley in 1953 and since then further developped by him into a theory. He considers the EEFL as the interface between the two portions of the vessel-blood organ. The theory concerns especially capillary permeability and transcapillary transport as well as interactions with perihemorheology (8,12,13).
- Coagulation and thrombus formation
- Thrombosis phenomena and rheological activation of cells (particularly platelets and leucocytes) and plasma proteins (such as fibrinogen).

The situations examined are usually highly complex and the rheological problems are further complicated by the accompanying physico-chemical and biochemical data. In particular, the conditions involved when moving from laminar flow regions to "vortex areas" should be the subject of detailed theoretical analysis, as the mechanical effects of turbulence play an important part both in the physico-chemical stability of the various cell components and of plasma as well as in blood vessel permeability.

4. EXPERIMENTAL FINDINGS IN HEMORHEOLOGY AND CLINICAL APPLICATIONS.

If hemorheology is to be an effective stimulant for rheology as a whole, it is essential that the experimental data should be meticulously established both in vitro and in vivo. When undertaking research on biological media and on living beings, a great deal of the experimental data available is often almost impossible to use as the basis of theoretical rheological treatments. This is due to the fact that in many cases the methods used are much too general to be capable of accounting for certain aspects of physical reality.

Moreover, the blame often lies with the manner in which the experimental data are interpreted. Indeed, the validity of the measurements is sometimes open to discussion because it is extremely difficult, when dealing with such complex systems, to isolate the criteria for reproducible experiments (14,15). An example of this are the numerous pathological microrheological changes in erythrocytes that have been described over the past few years and have been used as the basis for developing risky physiopathological theories. Although many of the experimental results most probably refer to objective phenomena, others are certainly connected with artefacts in the methods used (9,16,17,18).

One of the problems the experimenter will have to solve is precisely that of detecting which of the numerous variables observed are most suitable to be chosen as independent parameters that truly represent the phenomenon investigated. It is for this reason - given the complexity of the phenomena encountered in hemorheology - that experimental systems specifically adapted to the parameters that are to be measured will have to be developed, as no

pathological phenomenon can be treated rheologically if reliable techniques are not available. It is extremely satisfying to observe, however, that in spite of the many problems in hemorheology still outstanding, the informations now available can help the clinician to decide on hemorheological therapy. For example, the rheological origin of what is known as "hyperviscosity syndromes" and the part played by these syndromes in the occurrence of certain form of thrombosis has now been clearly defined according to the microrheological changes observed. It was in the light of these results that "hemodilution therapy" was suggested as a technique for treating hemodynamic disorders in patients suffering from peripheral arterial disease. The results further emphasize the major part played by the rheological properties of the blood (contents) in relation to the vessel (container) during blood distribution disorders and in the appearance of local ischemia. A large number of other recent clinical findings could also be mentioned. For example strict control of blood glucose level by means of an artificial pancreas in diabetic patients results in the return to normal ranges of the rheological parameters, with a parallel improvement in peripheral blood flow (13,19). Another example is the case of myocardial infarction and the "threat syndrome", where we have been able to demonstrate that there is a connection between the variations of the rheological parameters during the acute stage of the disease and the aggravation or improvement of the patient's condition.

5. CONCLUSIONS

As Biorheology (20,21), Hemorheology is a prime example of an interdisciplinary science which lies at the crossroads between mechanics, physics, engineering sciences, biochemistry, biology, clinical medicine and pharmacology. As is the case for all medical sciences, it is essential that clinical or pharmacological investigations should indicate the importance of rheological parameters in understanding pathological symptoms. I contend, moreover, that the highly original problems set by physiological flow patterns, cell behaviour and interactions between the blood and the vessel wall can act as an stimulation for fundamental rheology. It is only on this condition that the applications of hemorheological research will be included in their own right among the range of techniques applied in the clinical laboratories, on a par with cytological, immunological or biochemical methods.

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