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POISEUILLE AWARD LECTURE

BIORHEOLOGY, AN AGENT OF SCIENTIFIC PROGRESS

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Mr. Chairman, Ladies and Gentlemen

I am extremely sensible of the great honour which the International Society of Biorheology has done to me by the awarding of the Poiseuille medal, and I wish to share this honour with all my collaborators, in particular Dr. D. Bourgoin who is working with me from about thirty years. I am deeply grateful to Professor Silberberg and Professor Oka for their so friendly, warm and laudatory presentation of my scientific work. When I see this medal, I cannot forget that it has been designed by the great Icelandic artist Nina Tryggvadottir, the late wife of my dear friend Professor A.L. Copley.

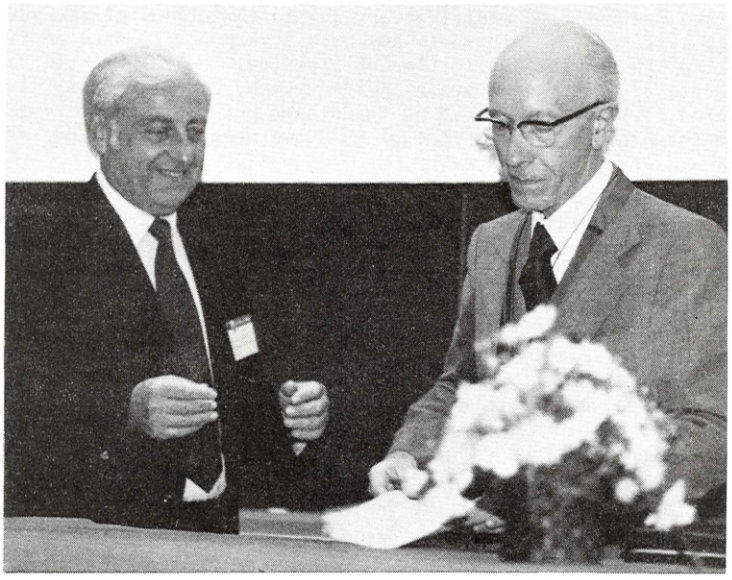

Fig. 1

Alex Silberberg with Maurice Joly just prior to his Poiseuille Award Lecture.

As I have the pleasure to give now the Poiseuille Award Lecture, I should like to submit to you some reflections on Biorheology.

It was only fairly recently that Biorheology became a well-defined and autonomous branch of science. The word biorheology was first introduced by professor Copley in 1948 to try to give a precise identity to a whole series of studies carried out at the frontier between biology and rheology. Biorheology does not limit itself to the application of rheological techniques to biological problems ; it is the study of the rheological properties of living systems and of their constitutive parts, of organized systems extrac-

ted from living systems, or of models of biological media. But official recognition of a specific identity for biorheology must not result in this new field becoming isolated among neighbouring sciences. It would be a great loss and mistake for the biorheologists to lose sight of the key role, the catalysing role which biorheology can play in the science development, by the questions it cannot fail to be asking other branches of science. I would like to give a few examples of this fecundating role of biorheology, to elucidate the reasons which lie behind it, and to indicate under what conditions biorheological research can properly fulfil its role.

It is a well known fact that the rheological study of liquids was the offspring of a problem of biorheology. For Poiseuille, the founder of viscometry, was primarily concerned with blood circulation in the lungs, and pathological anomalies in this system. In particular he wished to study the blood flow in the capillary vessels since he rejected the hypothesis of spontaneous movement of the blood cells (1).

The experimental physics which he developed, during the years 1839-1847, was a direct consequence of his desire to explain blood flow. The complexity of the phenomena in blood capillary vessels led him to study the flow of liquids under less complicated conditions, using simple liquids like water and solutions, in straight non-elastic tubes, an idea which was to have a very prosperous career : Poiseuille established what we know as Poiseuille's law, and the conditions for its application (2 - 4). Incidentally, it is amusing to note that whereas microcirculation of blood was at the origin of Poiseuille's research culminating in the establishement of his law, ironically enough this law is not valid for blood flow in capillary vessels.

This case of a medical man, transforming himself into a physicist in order to clarify a biorheological problem, is typical of the inciting role of biorheology. A major reason for this role lies in the nature of the object of biorheological research : it is indeed the very complexity of the biological systems, and sometimes the apparent strangeness of their rheological behaviour which oblige to undertake systematic researches in the most varied fields, thus advancing knowledge in different domains as a prerequisite to the solution of biorheological problems. In particular, in order to solve his problems, the biorheologist is very frequently asking questions which classical rheology, dealing with relatively simple systems, had not thought to be important.

For instance, what could be more complex than the system constituted by flowing blood and blood vessels, a kind of open system, thermodynamically speaking, which undergoes both qualitative and quantitative modifications due to variations of the surrounding media, and whose limiting surfaces are deformable and have a very complicated configuration ! Another factor which hinders the application of classical rheology to the case of rheology of blood is the scale of heterogeneousness in the system. The blood cell dimensions are macroscopic compared to the constituents of the plasma but microscopic compared to the dimensions of the large blood vessels, and of the same order of magnitude as the capillary vessel diameters.

Classical rheology on the other hand generally considers continuous and homoneneous media, the mobile units being infinitely small compared to the overall fluid volume which is distorted. Furthermore red blood cells can be deformed, and can also aggregate as superposed discs, the rouleaux, the aggregation kinetics being dependent on the flow conditions. In other words, we have here a very complicated suspension, highly concentrated, and in which there exists a correlation between structure and flow.

With intent to clarify the phenomena of flow deformation of blood cells and rouleaux, precise theoretical and experimental studies have been undertaken, chiefly in the laboratories of Professors Mason and Goldsmith since 1951, on much less complex, but very important, general problems such as the orientation, rotation and interaction of simple particles, spheres, rigid rods or flexible fibres, which were followed by the study of deformation and bursting of liquid drops, extension and buckling of elongated particles or strings of spheres or droplets under Couette flow.

Likewise, it is essentially for its importance in the blood circulation that so many theoretical researches have been undertaken on flow in low diameter tubes, researches which have furthered our understanding of numerous problems of classical rheology. Many authors have tried to determine by calculation a behaviour analogous to that of blood, but built up from classical fluid flow together with supplementary hypotheses. Some authors have studied as models monophasic flows of more or less complicated liquids. Diphasic flow has been introduced by several authors, the liquid mass being composed of a low viscosity newtonian layer in contact with the tube wall, surrounding either a newtonian suspension (5) or a non newtonian medium such as a Casson's liquid. This latter case has been studied under steady flow and pulse flow (6), leading to an expression for the newtonian layer thickness in terms of the Reynolds and Bingham numbers and the haematocrit (7). Important advances in theoretical rhéology have resulted from using models such as fluids with substructures, micro-polar or couple stress fluids, but not without much controversy (8). Nevertheless, many results were found by means of this theory. For instance : the coefficients of rotational viscosity and rotational gradient are increasing functions of the particle volume fraction ; inertia effects decrease compared to viscous effects when tube

diameter decreases ; and taking into account the deformable character of the particles, the exact solution for Poiseuille flow shows that abnormal effects such as the Fahraeus-Lindquist and Segré-Silberberg effects may be described by this way (9).

A very promising recent development, a very general theory of viscosity, for concentrated dispersions, proposed by Professor Quemada, also arose from an initial desire to represent the rheological properties of blood by equations whose mathematical parameters have precise relationships with physical structure elements. Using the principle of minimum energy dissipation, the solution of simultaneous equations for velocity and concentration profiles was attempted, the solution implying a coupling between the fluid and the particles in suspension. A change of flow brings about a radial displacement of the particles, thus a variation of local concentration and consequently variations of local viscosity which in turn will give a new change in flow. A variational method is used for minimisation of dissipated energy. The viscosity equation of a suspension which results from this analysis depends not only on rest conditions of the system but also on flow conditions. A very general formulation can be given which is obeyed by both newtonian and non-newtonian systems for a concentration range from zero to that corresponding to the maximum packing giving a rigid medium. Included in this formulation are structural parameters and coefficients such as relaxation time, which are necessary to account for variations in the equilibria association-dissociation, orientation-disorientation, deformation-non deformation. By introducing critical shear rates and reduced variables a convenient practical formulation may be obtained in terms of coefficients which are characteristic of the mechanical and physico-chemical parameters of the constituents of the suspension (10, 11).

In another field, numerous biological phenomena suggest the importance of the mechanical properties of the membranes of cells and intra-cellular organelles. As the membranes were long ago recognized by biophysicist as being systems of interfacial phases, it seemed reasonable to hope that a study of the rheological behaviour of bi-dimensional phases at interfaces would be a useful contribution to the understanding of membrane rheology. Nevertheless it seems that surface rheology, i.e. the rheology of monolayers has not yet come up to all results which one might have hoped for, with regard to the rheology of biological membranes. But, on the other hand, it has led to important results concerning the physical chemistry of interfaces, in particular the theory of interfacial phases.

Indeed, the systematic study, developed over the last forty years, of the surface shear viscosity, μ , of long chain aliphatic compounds at the air-water interface, as a function of the molecular area s and temperature, has shown that there are changes in the slope or curvature of the curves $\mu(s)$ corresponding to precise values of the molecular area for which singularities of both the compressibility modulus and the molecular electric moment are also observed. Second and third order transitions in monolayers have thus been demonstrated (12-13). Furthermore, it has beeen deduced that the molecules in a monolayer can only exist in a finite number of stable equilibrium states corresponding to discrete energy states and molecular areas (14, 15).

By applying Eyring's viscosity theory to monolayers the surface viscosity of newtonian layers can be expressed in terms of the surface molecular area and free energy of activation of flow which, in the case of condensed layers is very little different from the energy of activation of flow. This activation energy is the sum of that of the monolayer molecules distributed at rest in a quasi hexagonal lattice and that of the water molecules bound to these during their displacements. It can be calculated as a function of the interaction energy between these groups of associated molecules. Inversely, starting from the experimental values of surface viscosity one can deduce the molecular interaction energies for the different molecular states (14).

When there is distorsion under flow of the surface quasi-lattice, some molecules jump from their initial state to a metastable state corresponding to a smaller molecular area and higher interaction energy. The return to the initial state depends on a relaxation time which is an exponential function of this interaction energy. Under such conditions surface viscosity is non newtonian, μ decreases as the rate of shear increases (16). When the interaction energy is sufficiently high to give very high values of the relaxation time a great amount of molecules remains a long time in the metastable state, their number increasing with flow duration. At constant surface pressure the area of the monolayer decreases : there is a lasting transformation of molecular state induced by flow (17, 18). If the initial and metastable states correspond to immiscible molecules, they separate, and the flow induces a first order phase change (19). If the two molecular states are miscible, the decrease in area of the single surface phase is accompanied by an increase in surface viscosity, as greater as the shear rate is higher. These results can provide a useful model for interpreting, for instance, the shift of phase equilibrium due to flow observed in three-dimensional liquid systems such as certain high polymer solutions (20).

The study of the viscosity of protein monolayers has also led to interesting results. For each protein there is a surface pressure below which the monolayer is newtonian, and above which it is non-newtonian. The value of surface viscosity, when the non-newtonian region first sets in, is of the same order of magnitude for all proteins, this value being considerably lower than that of rigid molecules, taking into account the high

molecular areas of protein molecules spread on water. It can be deduced that protein molecules do not move as a black on the water surface but are deformed by the flow, since it has been shown that polypeptide chains do not dissociate into amino-acid residues when spread on water. From the experimental values of surface viscosity μ the surface area of apparent kinetic units can be determined, i.e. the area of rigid independent units which, if moving at the surface with respect to one another, would give under shear the same values of μ as the experimental ones. An area of about 90 $Å^2$ was found for all the studied proteins, much smaller than that of the polypeptide chains composing the protein molecules (21).

An analogous behaviour is observed with all high polymers which may be spread at an interface. For the same reason as given above, one can be sure that any molecule, which is undissociated when spread in a monolayer and which shows a surface viscosity for which the experimental activation energy of flow is less than that due to the bound water molecules, if calculated from total molecular area, are deformed in flow (22).

Thus we see that a research starting off as a tentative approach to a biorheological problem may end up as a thorough investigation of a chapter of physical chemistry.

Likewise, the study of the rheooptical behaviour of certain suspensions of biopolymers such as denatured globular proteins or tobacco mosaic virus, has led to an overall theory of the limited aggregation. Indeed, interpretation of the experimental results was only possible by considering that there are at each instant in the suspension aggregates the mean size of which depends on experimental conditions and undergone treatments.

A combination of Smoluchowski's floculation theory and Tobolsky's polymerisation theory extended to the case of association between particles leads to a general equation for the kinetics of aggregation-disaggregation (23, 24). The rates of association between two aggregates and of dissociation of one aggregate can be calculated in terms of mass and dimensions of the constitutive particles, potential barrier between two such particles, viscosity of the medium, shear rate and interaction energy between a particle and its neighbours in an aggregate. The average number of particles in an aggregate is obtained from the integration of the kinetic equation, and is given by experiment. Thus the interaction energy between the particles of an aggregate may be evaluated (25 - 27). The cases of globular and elongated particles have been fully dealt with, distinguishing between different types of systems : those without spontaneous aggregation ; those with a weak spontaneous aggregation, and finally those with a high spontaneous aggregation but not resulting in either floculation or precipitation. This general theory of limited or temporary aggregation is applicable to the blood suspension, and provides a means for determining the interaction energy between the blood cells in the rouleaux using data obtained by light retrodiffusion technique for instance (28).

In many other fields of science there is no doubt that biorheological phenomena, with the complex problems that they pose, have been at the origin of important developments. This is particularly true in biochemistry. It is perfectly obvious, for example, that it was the unexpected rheological properties of the sickle cells in the absence of oxygen which triggered off a whole series of investigations on S hemoglobin, resulting in the discovery that the only difference with normal A hemoglobin was the substitution of a valine for glutamic acid in the sixth position on the β chain, this discovery leading in its turn to innumerable works on abnormal hemoglobins. In a similar manner it was the curious rheological behaviour of the muscles which heightened interest in the studies of the microscopic and submicroscopic structures of muscle fibre, which in turn brought about a considerable development in the biochemistry of muscle proteins. And once again the surprising flow phenomena in the protoplasm were largely responsible for the studies on the protoplasmic microstructure and on biochemistry of many cytoplasmic proteins. The relation between metabolism and rheological properties is a subject which is far from being completely worked out.

Let us now examine the conditions which present-day biorheological research must fulfil if it is to continue to be a catalyst, an instigator of new works in other scientific fields.

Obviously it is necessary that a wide variety of subjects should be examined by the biorheologists, but above all they must discipline themselves to a very rigorous methodology for their work to have a real impact in other fields. New facts must be proved incontestably, the parameters of the studied systems must be clearly enounced, the experimental conditions given in detail.

Skill and intuition must be used in detecting which variables of the studied system are in fact measurable quantities, i.e. stationary quantities or the values of which are extrema with respect to neighbouring quantities of the same nature, and care must be taken to verify that the characteristics of the measuring equipment allow significant results to be obtained for the measured quantities (29, 30).

Even more critical is the task of determining what are the independent parameters in a given phenomenon. For this one cannot choose arbitrarily a parameter which in the mathematical equations could be an independent variable ; in order to gain an insight into

the physical meaning of the observed phenomenon one must choose parameters which appear to be at the start of the various causal chains. And when one eliminates certain of these independent parameters as playing a negligible role, such a process should be considered as temporary, as it may simply be that the equipment used is not sufficiently sensitive to detect their real influence.

The research worker must always be concerned with obtaining reproducible results, but remember also that non-reproducibility has often given a clue to the existence of hidden parameters, leading sometimes to a completely new understanding of a phenomenon and even to the discovery of new phenomena.

Systems of biological interest are in general characterized by the extreme complexity both of their structure and of their rheological properties. Consequently classical rheological models only give a very rough approximation of the observed behaviours and their elements can rarely be associated in a satisfactory way with the components of the studied systems. Furthermore, generally valid fundamental equations for such systems are very difficult to put in a form in which the rheological parameters employed have some sort of physical significance and do not remain purely abstract. And it is perhaps this incapacity of classical rheology to provide satisfactory answer to biorheological problems which has forced the biorheologist to seek for solutions in other disciplines outside of mechanics, so as not to remain on a purely descriptive level. This is why, in my opinion, the most fruitful line of research for Biorheology lies in seeking with an ever greater precision the causes of observed rheological behaviours, rather than in increasingly rigorous mathematical representations.

To finish this lecture I should like to give a few suggestions (31) concerning the rheological study of systems which, like biological ones, depend on a large number of parameters and have a wide range of rheological properties which vary according to the experimental conditions. Such systems may be refered to as "rheologically hypersensitive or hypervariable". To simplify I will limit myself to the case of the study of the stress in a Couette flow of such a system.

Stress measurements may be carried out in a wide variety of experimental conditions : as a function of apparent shear rate, over a certain range of shear rate, after a given flow time, at constant temperature and for a first shearing experiment ; as a function of time with constant shear rate and temperature ; in both the above cases but at different temperatures ; successive experiments at fixed time intervals ; the flow conditions being steady, or harmonic or transient with rectangular or triangular steps of rate of shear, etc... In order to exploit such a complex mass of experimental data a succession of approaches of increasing difficulty must be followed.

Firstly, only the results obtained for which all independent parameters except one have been maintained constant must be taken into consideration. Temporarily this parameter is taken as the principal parameter and studied over the limited range in which the observed behaviour corresponds to that of a simple rheological body, and for which one can thus determine rheological coefficients such as viscosity, elastic modulus, retardation time and relaxation time. In the narrow zone considered the real system may then be represented by this simple rheological body. The coefficients so determined are only "apparent" in the sense that they are relative to a certain type of experiment and over a limited range of variation of the chosen parameter, and furthermore because they are characteristic of a fictitions system (the considered simple rheological body) which is only locally "tangent" to the real system (32). They have, therefore, no intrinsic significance for the real system.

The next step, after having chosen a simple rheological body tangent to the real system, is to consider the whole group of tangential systems over the whole range of variation of the considered independent parameter, and to establish the laws of variation of the apparent rheological coefficients as a function of parameter.

In the choice of the simple rheological body whose behaviour is tangent to that of the real system over a particular range of variation, - Maxwell, Kelvin-Voigt, Bingham bodies, etc... - one must be guided by the general form of the rheological behaviour observed, and the relative simplicity of the laws which then describe the variations of the apparent rheological coefficients.

The third stage consists in repeating the above operations successively for all the other independent parameters in order to deduce the laws describing the variations of the rehological coefficients which can be associated with each parameters. An attempt must then be made to interpret these relations in terms of the structure of the system and of its variations as a function of the various parameters. In other words one must try to find a physical significance for the different apparent rhéological coefficients in order to establish behaviour equations which will contain rheological coefficients having an intrinsic character, specific to the studied system, either at a microscopic or submicroscopic level. For example, in order to interpret memory effects or evolution functions of the apparent macroscopic rheological coefficients, one could bring in the kinetics of spontaneous or flow induced structural modifications.

In passing from the macroscopic to the microscopic level, the choice of the

volume element, introduced in rheology from the mechanics of continuous media, is important. In biorheology, this choice must be such that each elementary component of the studied system exists at each moment inside the volume element practically in the same proportions as in the bulk of the system. In other word, each volume element is a multiphase system whose rheological properties depend on those of the microvolumes occupied by each of the constitutive structural elements in accordance with the "microrheological" model proposed by Professor Axelrad (33, 34).

Ideally, the ultimate step would then be to group together all the possible types of rheological behaviour exhibited by the studied system in an equation of state containing the intrinsic rheological coefficients expressed as a function of the characteristic physico-chemical parameters of the system. Of course, in many cases this remains a far off ideal ! This should not discourage the biorheologists, but should rather stimulate their researches, for even if the intellectually satisfying overall representation of the rheological behaviour seems far off, they do know that already at the level of the 2nd and 3rd steps described above, the effort to include the problems of microstructure and intermolecular and inter-particle interactions in their preoccupations will bring about considerable progress in the understanding of biorheological phenomena and provide many stimuli for other kinds of researches. The biorheologists having thus made their contribution, they may leave it to the biochemists, biophysicists, and molecular biologists to try and discover some of the initial causes which lie behind the rheological behaviour of living systems.

I thank you for your kind attention.

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