BIORHEOLOGY, 26; 423-461, 1989
0006-355X/89 $3.00 + .00 Printed in the USA.

THE ROBIN FÅHRÆUS MEMORIAL LECTURE*

ROBIN FÅHRÆUS - THE SCIENTIST AND THE PERSON

Alfred L. Copley

Laboratory of Biorheology, Polytechnic University
Brooklyn, New York, 11201, USA

* Presented on 1 December 1988 in Stockholm, Sweden

1. INTRODUCTORY REMARKS

I should like to thank Professor Lagerlöf and the Swedish Society of Pathology for kindly inviting me to give the Robin Fåhræus Memorial Lecture at your Society's Annual Meeting in connection with the Annual Assembly of Swedish Physicians, 'Riksstämman', here in Stockholm. I feel deeply touched to have been chosen to honor my friend Robin Fåhræus on the occasion of his hundredth birthday and to address this august Society, whose members have so greatly advanced the biomedical sciences towards aiding and serving the ill of the community of human beings everywhere.

One of the great medical scientists among the distinguished members of your Society was Robin Fåhræus. I have been very fortunate to meet with him on several occasions during the past ten years of his life at scientific congresses and biomedical conferences, and I felt privileged to become one of his friends.

As many among you, I sensed deeply his stature as a scientist and his integrity, warmth and humor as a person. The more I became acquainted with his works, the more I became aware of the significance of his scientific contributions to the advancement of medicine. What amazed me was not merely the breadth of knowledge or his scholarship pertaining to the history of medicine. It was his grasp of what signifies the advancement of science. Moreover, I was impressed by the profundity which illuminated his insights.

This lecture is divided into several parts. First I should like to acquaint you briefly with Robin Fåhræus, the historian. This will be followed by an account of his scientific contributions with emphasis on hemorheology. I shall attempt to place these contributions as they concern hemorheology in context with early and most recent developments in experimental and clinical hemorheology, of which Robin Fåhræus was a master. It is meant to demonstrate the impact of his findings and thoughts on the present status of hemorheology. Then I should like to acquaint you with the role Fåhræus played in the development of biorheology as an organized science (1). I finally shall give a picture of Robin Fåhræus as a person.

2. HISTORICAL STUDIES

Robin Fåhræus is known for his many studies regarding the history of medicine. His 'History of Medicine' was published in three volumes in Swedish (2) and in a Spanish edition (3). I understand that there are no other translations. Certainly, it will be helpful to those interested in the history of medicine to have these volumes published in English and other languages. One historical account concerned Carolus Linnaeus (1707-1778), who practiced medicine and is known as the founder of modern systematic botany. In 1957, Fåhræus presented the 250th Anniversary Lecture of Linnaeus' Birth (4).

Recently, Patrick Sourander cited in a biography of Robin Fåhræus an excerpt from a letter I wrote on 16 May 1963 to Robin Fåhræus (5). My letter was in response to his communication, entitled: 'Archaic Hemorheology. The Early Historical Significance of Blood Sedimentation' (6,7), which he gave at the Symposium on Biorheology during the 4. International Congress on Rheology, at Providence, RI, USA, in 1963. It sums up what I continue to think about Robin Fåhræus as a historian. I wrote to him: 'There is no one who could talk on this topic as expertly and with so much authority as you for all reasons, not the least that you have retrieved it from hidden places of ancient medicine and have shown its importance to the world. I have always admired the brilliant scholarship and depth of your historical treatises and I, for one, will always be grateful to you that you, among only a few others, have taught me to appreciate the history of science and its significance in contemporary scientific research and, in general, in the position of modern man.'

I shall not dwell on the historical findings by Fåhræus in this lecture, but I like to emphasize that he was very much aware that hemorheology was one of the earliest fields in the history of medicine.

The importance attached to the heart and blood goes back to observations made in prehistoric times as shown in cave paintings of bison and other mammals. The position of the heart is pictured by a mark or colored spot in these paintings, which may have served to instruct the huntsman where the victim is most vulnerable. The fading out of life in the flow of blood from a fatal wound must have been associated by prehistoric man with the idea of life (8).

Fåhræus gave several accounts of humoral pathology of antiquity (6-12). He correlated humoral pathology with the increased erythrocyte sedimentation rate and its significance. In numerous examples he pointed out how the clinical observations of physicians since the 5th century fitted into the conceptions proposed already by Hippocrates at about 460 B.C. with regard to various diseases.

Fåhræus pointed out that the pathology of the ancient Greeks was founded on observations of the blood. To them the contents of the venous system appeared to be a mixture of four fluids, which separated more or less when this mixture had left the warm body. These fluids were known as the black bile, the yellow bile, the 'blood' (in the limited sense of the word) and the phlegm. In the conception of disease our early Greek ancestors considered the properties of the phlegm to have the greatest influence. Although the phlegm was invisible in normal blood, it formed a more or less thick layer in the top of clotted blood. Fåhræus emphasized that this phenomenon was a consequence of increased blood sedimentation. However, the Greeks took this phenomenon as proof that 'the phlegm had increased in amount, a change of the contents in the veins much more ominous, as the phlegm in contradistinction to the other three fluids had the property to congeal and make the contents of the vessels immovable' (6,7). They thought that the fever was nature's means of counteracting this tendency. Physicians considered venesection as the most effective way of reducing the predominance of phlegm, which was named the 'crusta inflammatoria'. It was thought, since it was first proposed by Hippocrates in his most celebrated text 'On the Human Nature' (6,7), as the theoretical foundation for massive bloodletting in disease. There was subsequently in the history of medicine a most horrible abuse of this treatment.

Fåhræus emphasized that there were two categories of subjects who became special victims of this generally accepted therapy of bloodletting (6,7). Blood from healthy pregnant women had this buffy coat, the 'crusta inflammatoria', due to increased blood sedimentation. They were subjected to great losses of blood, which, in combination with the delivery, became deadly perilous. Fåhræus considered horses to belong to the other unhappy category. These animals have normally very intensive rouleau formation of erythrocytes with consequently a high sedimentation rate. Fåhræus mentioned that more than a century ago horses, belonging to the Swedish Army, were gathered in so-called bleeding meetings. The impact of this therapy in patients continued until the beginning of the 19th century until two great French physicians François-Joseph Victor Broussais (1772-1838) and Jean Baptiste Bouillaud (1796-1881) fought against this practice and succeeded to stop it. This involved particularly the treatment of pneumonia, where patients were subjected to daily and copious blood-letting of up to about two-and-a-half liters. Fåhræus emphasized that what appeared to be most promising for the patient and physician was that there was an improvement of short duration. However, as Bouillaud found at the Hôpital de la Charité in Paris, the rates of mortality of the group of patients tripled. The rate of mortality of a control group of patients, who received only

homeopathic treatment, was about one-third of those treated by the practice of venesection (6,7).

Nevertheless, Fåhræus concluded that, in their observations of the blood, the ancient Greek physicians were right and presented the first steps in the direction of what we have now as medical science.

In the 18th century, it was, according to Fåhræus (12), the English physician William Hewson (1739-1774), who pointed out in 1772 that 'the inflammatory crust or size is not a newly formed substance, but is merely the coagulable lymph separated from the rest of the blood'. Fåhræus also credited Hewson in proposing that increased sedimentation velocity was the most important factor in the production of the inflammatory crust.

3. SCIENTIFIC CONTRIBUTIONS WITH EMPHASIS ON HEMORHEOLOGY

3.1 Non-Hemorheological Studies

Fåhræus was the co-author with The Svedberg of the new method for the determination of the molecular weight of proteins (13). According to Sourander and Breimer (3), it was Fåhræus who suggested the use of hemoglobin for the first successful attempts to determine the definite molecular weight of a protein molecule, employing the newly constructed optic ultracentrifuge.

There are other non-hemorheological studies by Fåhræus, which I shall not discuss here. They include investigations on glycogen formation in surviving liver tissue (14), as well as on acid phosphatase of the erythrocytes (15).

3.2 Some Definitions

Rheology is a physical science, which was organized in 1929 in Washington, DC. It denotes the deformation of matter including flow. As a non-biological science, it was limited to anomalous flow properties of substances or systems which do not obey Newtonian Law and are named usually non-Newtonian fluids.

Biorheology is a term which I introduced in 1948 in a plenary lecture on Rheological Problems in Biology at the I. International Congress on Rheology (16). I cannot give here an account of the development of this modern life science. Contrary to rheology, it deals both with Newtonian and non-Newtonian biological fluids of importance in life processes. Biorheology is considered as the link between most, if not all, life sciences (17), since in biological systems there is deformation and flow. However, as emphasized by Silberberg and Copley, unlike straight rheology, biorheology is concerned not only with the 'how' but also and predominantly with the 'why' biological materials behave as they do. The rheological properties of biological materials are 'inextricably linked to the transport and motility requirements and thus to the molecular, structural and thermodynamic description of the biological system' (18).

'There are fundamental tasks facing biorheology asking it to

provide the understanding for why Nature built in the way it did, particularly why certain structures and organizations, using certain materials and dimensions, have evolved.' Much more feeds into biorheological study than the rheological characterization of a biologically derived material. 'Since movement and the accompanying transfer of energy is the essence of life processes, problems of deformation including flow lie particularly close to the center of things insofar as living matter is concerned' (18). Thus, biorheology is bound to cover, as a scientific discipline, all kinds of life processes.

Hemorheology continues to be the most active field of biorheology. It concerns not merely the flow properties of blood and its constituents, but as well the vessel wall with which blood comes into direct contact and the exchanges between the blood and the tissues via the blood vessel wall. The vessel wall and the blood have been conceived since 1960 as an entity (19). Recently it was considered as an organ, named the 'vessel-blood organ', penetrating all other organs (17).

Hemorheology is closely associated with the rheology occurring in the perivascular spaces, across the parenchymal cell membranes, and that of the lymph, its channels or lymphatics and there walls. The term 'perihemorheology' was introduced in 1987 for this field of biorheology (20). Perihemorheology deals with the exchanges of rheological processes between the vessel-blood organ and its surrounding tissues, as well as in reverse.

3.3 The Swedish Protein Molecule - A Milestone in Modern Hemorheology

In the development of modern hemorheology, there are two Swedish scientists who have contributed greatly to advance this field. Olof Hammarsten (1841-1932) isolated fibrinogen and demonstrated its importance in the formation of fibrin by the action of thrombin on it. Robin Fåhræus found fibrinogen to act as vehicle in erythrocyte aggregation, thus affecting the viscosity of blood.

Rudolf Virchow, who introduced in 1847 the term 'fibrinogen' for a clottable substance (21), did not consider it as a precursor of fibrin. However, it was Denis de Commercy (22) who, in 1859, was the first to recognize that plasma contained a clottable substance from which fibrin originates. Denis designated this precursor of fibrin by three different words, viz., 'plasmine', 'sérofibrine', and 'fibrinogène'. Alexander Schmidt, who was a student of Virchow and who later became Professor of Physiology at Dorpat, discovered thrombin, which converts fibrinogen into fibrin. However, it was Hammarsten, who, in a series of papers on the biochemistry of fibrinogen and its purification, succeeded in recovering the plasma protein fibrinogen. His work demonstrated that the formation of fibrin was the specific result of the interaction between thrombin and fibrinogen.

Hammarsten clarified that in the transformation of fibrinogen to fibrin, the latter was not formed from two plasma proteins as Schmidt believed, viz., fibrinogen and what was called

'paraglobulin'. In contrast to Schmidt's contention, he found that thrombin acts solely on fibrinogen in its conversion to fibrin (23,24). Moreover, Hammarsten suggested in his communications from 1876-1880 that there might be a hydrolytic cleavage of the fibrinogen during coagulation. This suggestion was based on his previous work on casein, in which he demonstrated that, in the presence of rennin, a cleavage of the protein occurs (25). Furthermore, Hammarsten suggested in 1876 the importance of the salt concentration for fibrin formation. However, he was not aware that calcium is important for thrombin formation, as was discussed by Arthus and Pagès in 1890 (26).

The conditions under which a fibrin clot formed were clearly defined by Hammarsten, but he was cautious in trying to explain the mechanism (25). Thus, the credit goes to Hammarsten for establishing fibrinogen as the precursor of fibrin. Hammarsten wrote between 1876 and 1902 a series of papers on the biochemistry of fibrinogen. He could not have foreseen the role of fibrinogen in the aggregation of erythrocytes, which was later demonstrated by Fåhræus.

The work by Fåhræus on suspension-stability of blood, as he named it (12), emphasized its role in many disease processes. Although the methods of erythrocyte sedimentation by different investigators could not establish them as pathognomonic tests, they introduced into biomedical thinking in this century the importance of biorheological testing in clinical conditions. There is now a growing number of hemorheological and other biorheological approaches, which are designed to serve the diagnosis, therapy and prognosis of many different disease processes (27-30).

It appears to me to be most intriguing that it was here in Sweden, where basic observations were made concerning the roles of fibrinogen. As mentioned above, neither fibrinogen nor the aggregation of erythrocytes, in which fibrinogen so directly interacts, are concepts which originated in Sweden. However, it was here where the significance of these milestones in modern hemorheology was actually established. Fibrinogen may thus well be designated as the 'Swedish Protein Molecule'. As it is the first protein ever isolated, this designation becomes particularly meaningful. The 'Swedish Protein Molecule' will continue to be preeminent in the future of medical science.

3.4 Experimental Hemorheological Studies

3.41 Some Basic Experimental Studies Antedating Those by Fåhræus

The experimental hemorheological investigations by Fåhræus were made extra vivum with rather simple techniques. They concern mainly erythrocyte sedimentation, the role of fibrinogen in erythrocyte rouleau formation, the flow of blood in glass capillaries of very small diameters, the erythrocyte-plasma interface as related to the physiology of the spleen, and erythrocyte filtration.

Before giving a brief account of the experimental hemorheological studies by Fåhræus, it appears appropriate to

hemorheological studies by Fåhræus, it appears appropriate to mention some basic experimental studies antedating the work by Fåhræus.

Blood does not obey Newton's law for ideal fluids, as it is a suspension of blood cellular elements in plasma. Hess noticed in 1915 (31), that the blood obeys Newton's law only at high flow and shear rates. However, this is an exception since, otherwise, blood has non-Newtonian behavior (32). The French physician Jean-Léonard-Marie Poiseuille, who lived in Paris from 1799-1869, studied the flow of blood in the microcirculation of different animals. He established from his subsequent experimental studies of the viscosity of water (33), what is known as the Poiseuille equation.

Hagen in Germany found by experiment in the 1830's and Poiseuille nearly at the same time (8) the law that relates V, the volume (ml) flow per second, to R, the tube radius (cm), L its length (cm) and P the pressure drop (dynes/cm^2) across the tube. Taking Isaac Newton's assumption that the 'lack of slipperiness' or, as we now call it, viscosity, η, is measured at low speeds by the constant ratio of force to rate of flow, it was later shown that the equation can be calculated, making only a few simple assumptions about limiting conditions. The equation is:

$$V = \frac{P\pi R^4}{8 L \eta}$$

As pointed out by Scott Blair, corrections for very precise work must be added to allow for anomalies at the ends of the capillary and for changes in velocity at the entrance (34).

When, as reported in 1842, Poiseuille tried to apply his equation to the flow of blood in glass tubes with diameters differing from 0.194 to 0.256 mm, his equation was not applicable. The reports by investigators, such as Duncan and Gamgee in 1871 (35), who measured blood viscosity in glass tubes, could also not establish the Poiseuille equation to be generally valid for blood.

As Poiseuille did not understand the non-Newtonian behavior of blood, it may be the reason why he abandoned, about 145 years ago, further studies on blood viscosity. Nevertheless, both his in vivo hemorheological investigations of the microcirculation, as well as his painstaking studies on the viscosity of water, remain milestones in the history of science.

Studies on the axial accumulation of blood cells were reported by Poiseuille from 1835 to 1839 (36,37). He observed biomicroscopically in animals that the axial stream of erythrocytes in capillary blood vessels was separated from the wall of the vessel by an annular sheath of plasma, the marginal or plasmatic zone. Poiseuille demonstrated that the width of this marginal zone, referred to in the French literature as 'zone de Poiseuille', depended on the velocity of the flow of blood. He also concluded that the fluid in the plasmatic zone comprised a series of layers, the velocity of which decreased progressively to zero at the vessel wall. When the rate of blood flow was increased, the plasmatic

zone became wider, as Copley and Staple confirmed in the microcirculation of the cheek pouch of Chinese and Syrian hamsters, as reported from 1959 to 1962 (37). Poiseuille also observed this axial accumulation in glass tubes, which was confirmed in 1868 by Schklarewsky (38), and referred to by Fåhræus in 1928 (39).

In 1839 Poiseuille proposed that the plasmatic zone in the circulation of the blood in vivo consists of two portions, viz., a wide mobile portion and, in close proximity to the vessel wall, a very narrow immobile portion (37). Copley and Staple (37) provided experimental evidence to some extent for the existence of the immobile portion of the plasmatic zone. They proposed that in this more or less immobile portion the continuous processes of fibrin formation and fibrinolysis can occur undisturbed by the flow of blood. To these continuous processes Copley added more recently fibrinogenin formation and fibrinogenolysis (40,41).

3.42 Intravascular Erythrocyte Aggregation and the Distribution of the Leukocytes in the Vascular System

Fåhræus gave several historical accounts of the work on increased sedimentation velocity of erythrocytes. He mentioned his accidental observations in 1917 (42) on increased erythrocyte aggregation occurring in pregnancy. This kept his interest during his entire scientific career.

Although Fåhræus' lifelong work was closely associated with the intravascular aggregation of erythrocytes, he limited his studies to observations of the flow of blood in glass tubes. He considered that there 'are two different factors which alone or together give rise to visible aggregation in the small vessels, namely an increased tendency of the erythrocytes to aggregate and a slowing down of the blood stream' (43).

Fåhræus emphasized that 'the size of the particles of a suspension, streaming through a narrow tube, has a decisive influence on their position in the stream, the greater particles being more effectively transported in the axial stream than the smaller ones, thus giving rise to a broader marginal stream'. As the leukocytes are larger than the erythrocytes, they normally migrate towards the rapid axial stream. However, with increased rouleau formation they migrate towards the slow marginal stream. A certain amount of leukocytes is consequently transferred from the large vessels to the small ones (39,44). Fåhræus pointed out that Vejlens, a pupil of Fåhræus, found injections of fibrinogen or gelatin into rabbits to increase the rouleau formation in the small vessels, giving rise to a more contracted axial stream of the erythrocytes and a broader marginal plasmatic zone rich in leukocytes. As emphasized in 1922 by Jeffery (43,45), a suspension would flow through a tube with a minimum dissipation of energy, if the particles were concentrated as closely as possible about the axis of the tube in the region of minimum shear.

3.43 The Suspension-Stability of the Blood and the Vehicular Function of Fibrinogen

In his article 'The suspension stability of the blood',

published in 1929 in Physiological Reviews (46), Fåhræus deals with this phenomenon in considerable detail. He applied the law of Stokes concerning the hydrodynamics of the sedimentation of spherical particles, suspended in a fluid of less specific gravity than the particle itself. In his microscopical studies of fresh drops of blood from healthy human subjects, Fåhræus found that the erythrocytes are aggregated to a certain extent. This aggregation presents a 'characteristic architecture, because the corpuscles unite with their flat sides against each other forming what has been called piles of coins or rouleaux (Geldrollen). But the rouleaux in healthy blood usually do not contain very many corpuscles; they are somewhat irregular in form, do not show any great tendency to join together and consequently appear quite evenly distributed' (46).

Fåhræus made observations on blood from severely diseased persons as well as pregnant women which, however, give quite another appearance in that the rouleaux contain, on average, many more corpuscles and these rouleaux are more closely and regularly united with each other. Moreover, the greatest difference is that the rouleaux are clustered to a very high degree and separated by large lakes of free plasma. These aggregates or rouleaux are also larger in pathological blood and show a more solid structure. Fåhræus observed that a 'parallelism exists between the tendency to rouleau formation and sinking velocity.' He asked 'whether the increased aggregation tendency of the erythrocytes is due to changes of the cells themselves, or to changes of the plasma.' Although Fåhræus contends that increased aggregation is determined by a change in the surface layer of the erythrocytes, the stability of the suspension 'is mainly dependent upon the properties of the fluid medium' (46).

Fåhræus provides experimental evidence that 'the plasma contains substances which are the vehicle of its aggregation capacity - substances presumed to increase in pregnancy and disease.' He proved further that 'the rouleaux formation in normal as well as pathological blood is caused by the hydrophil colloids of the plasma, the proteins, and that the degree of aggregation depends upon these proteins being altered in amount or properties during pregnancy and disease.' In several experiments he confirmed the observation made by Hewson over 200 years ago that the fluid medium of the blood furthers aggregation and the sinking velocity, a result which has been confirmed by many later investigators (46).

It was Fåhræus who thought that the substance in the blood with the capacity to aggregate erythrocytes is mainly fibrinogen and to a lesser extent 'serum-globulin'. Fåhræus considered fibrinogen to be the 'vehicle', the word he actually used, which aggregates erythrocytes in the formation of rouleaux (46).

3.44 The Fåhræus-Lindqvist Phenomenon and the Fåhræus Effect

Fåhræus and Lindqvist reported in 1931 their findings of blood viscosity in very narrow glass capillaries with diameters which differed from 0.505 mm to 0.040 mm (47). They found it not to be constant but to depend on the diameter of the tube. Below a critical point, at a diameter of about 0.3 mm, the viscosity

decreases markedly with the reduced diameter of the capillary. This is called the 'Fåhræus-Lindqvist phenomenon'. It should be noted that, unknown to Fåhræus and Lindqvist, the same phenomenon was already observed in non-biological fluids as early as 1919 by Bingham and Green (48) working on paints, but these authors did not study the phenomenon quantitatively. Beginning in 1930, Schofield and Scott Blair made an intensive study of this phenomenon in soil and clay pastes which they named the 'sigma phenomenon' (48).

The 'Fåhræus Effect', so-named by Barbee and Cokelet in 1971 (49), is based on observations by Fåhræus, published in 1929 (46). He found that when blood flows from a tube with a large diameter through a capillary tube, the average hematocrit of blood in the capillary is less than that of blood in the large diameter tube.

3.45 The Erythrocyte-Plasma Interface and the Physiology of the Spleen

In 1939, Fåhræus (50) discussed the erythrocyte-plasma interface and its changes regarding decreased rouleau formation and spherocytosis, 'alterations in direction of hemolysis - and as regards the plasma in the formation of lysolecithin by a serum-lecithinase similar to that in cobra venom'. He considered the changes to take place in the spleen which acts as 'the separator of the blood'. The erythrocytes are kept there 'deplasmatised' in the venous sinuses of the spleen according to Knisely (51,52).

Fåhræus considered hemolysis to take place 'when separated blood components reunite in the splenic vein' (50). He considered the fact that the circulating blood maintains its properties depending 'on the fact that the stabilization process in the erythrocytes is prevented or its effect neutralized by the plasma and vice versa - an interaction which must be located at the erythrocytes-plasma interface' (50). Fåhræus contended that 'the area of this interface may be diminished not only in the spleen but also in the circulating blood, with effects upon its fat metabolism' (50). This diminished area of this interface may occur either by the reduction in the number of erythrocytes or by increased rouleau formation. He concluded that the intravascular phenomenon of increased rouleau formation causes the increased sedimentation rate in diseases as well as in normal pregnancy.

Robin Fåhræus kept his particular interest in the spleen, the roles of which he discussed in a paper, published in 1963 (53). He referred to Galenos who called the spleen 'plenum mysterii'. What excited Fåhræus' interest particularly was the reported rarity of primary and secondary tumors in the splenic pulp. Fåhræus referred to a morphological peculiarity of the splenic blood, already mentioned by Hammarsten in 1883 in his 'Textbook of Physiological Chemistry' (53,54). This peculiarity concerns the finding that the erythrocytes from the spleen are less flattened than in blood from other parts of the vascular system. This observation was also later published by Heilmeyer in 1936 (53,55) and, in the same year, by Bergenhem and Fåhræus (56).

Another observation, also mentioned by Hammarsten in the same

Textbook, was that the rouleau formation of erythrocytes is reduced in the blood of the spleen (53,54). Fåhræus made a study of blood, stored extra vivum at body temperature, and found the same morphological changes. Originally, the erythrocytes appear closely packed in typical rouleau formation. However, after several hours they become thicker and their diameter is reduced, resulting in their appearance as complete spheres with highly reduced tendency to aggregate. Parallel to these changes, the erythrocyte sedimentation rate is markedly reduced (53).

Fåhræus (53) concluded that the blood stored in the spleen or extra vivum at body temperature undergoes the same changes. He considered that the osmotic concentration in the interior of the erythrocytes is increased, 'at least partly by decomposition of organic phosphorus compounds'. He emphasized, as a consequence, their volume is increased and their osmotic resistance reduced.

3.46 The Fåhræus Erythrocyte Filterability Test

In the last decade of his life, Fåhræus reported experimental studies for which he developed the erythrocyte filterability test and designed an apparatus. He presented his findings in 1958 at the 3. International Congress on Rheology at Bad Oeynhausen (57). Fåhræus studied with this method, in comparison with the erythrocyte sedimentation rate, the blood of healthy animals and human subjects as well as of patients afflicted with different diseases. He emphasized the importance of the pore size of the filter paper for his test. He drew the curves for the evaluation of his findings, which showed the distribution of the erythrocytes in the pile of the six filter papers employed in the test, and thus demonstrated the different degrees of erythrocyte aggregation.

It may be of interest that the Fåhræus Erythrocyte Filterability Test was apparently not known to many hemorheologists who, about a decade later, began to study the filterability of erythrocytes with filter paper for another purpose, namely to determine the flexibility of the erythrocyte membrane. Nevertheless, it was Fåhræus who pioneered the use of filter paper in experimental studies concerning rheological aspects of erythrocytes. This I pointed out eight years ago at the banquet of the International Symposium on Filterability and Red Blood Cell Deformability, held in Göteborg in 1980.

3.5 Clinical Hemorheological Studies

The pathophysiology of the circulation of the blood gained immensely from the findings by Fåhræus and from his thoughts. It is not possible to give here a detailed review of them, but I shall present briefly a small selection.

Fåhræus presented his erythrocyte filtration test also in a paper (58), published in 1962. He emphasized that the embolic effect of erythrocyte aggregates probably explains the principal clinical symptoms of eclampsia, the convulsions and the coma. Indeed, he observed that the injection of a suspension of Lycopodium spores into the left ventricle of the heart of rabbits resulted in convulsions and coma, followed by death (58,59). He

used these findings in rabbits, published in 1960, as a model for the embolic effect of erythrocyte aggregates to explain the principal clinical symptoms of eclampsia.

In addition to the hyperinosis (i.e., increased fibrinogen content in the circulating blood) and increased aggregation of erythrocytes, Fåhræus listed other processes involved in the pathogenesis of eclampsia, viz., hypoxemia, increased permeability of the capillary wall, hypertension with edema, erythrocytosis and hemolysis. He pointed out the possibility of close causal connection between hemolysis and increased fibrinogen content of the plasma. Fåhræus concluded that the so-called hyaline thrombi found in the first phase of eclampsia are identical with erythrocyte aggregates.

To Fåhræus, 'it did not seem unlikely that tumor cells in stored blood are damaged in the same way - a possible explanation of the rarity of primary and secondary tumors in the spleen' (53).

Fåhræus established that increased erythrocyte rouleau formation occurs during normal pregnancy, but it becomes further increased in eclampsia. The formation of large solid erythrocyte aggregates act as thrombo-emboli, and, in his view, explain the fundamental disturbance of the circulation in eclampsia.

With his studies on 'The Suspension-Stability of the Blood', reported as a thesis in 1921, Robin Fåhræus (12) handed to the medical profession a tool, the erythrocyte sedimentation rate test. It is a simple procedure for which several authors developed different methods. These clinical erythrocyte sedimentation tests, although non-specific, are employed all over the globe and serve as an aid to the practice of medicine and surgery.

Fåhræus accomplished far more than the initiation of measurements of the erythrocyte sedimentation rate. He made the medical profession aware of the usefulness of clinical hemorheological procedures. Fåhræus thus prepared the minds of physicians and surgeons for other clinical hemorheological tests, developed ever since.

3.6 Hemorheological Studies by Others in Context with Those by Fåhræus

There are numerous publications in the literature in context with the hemorheological studies by Fåhræus. I shall here again limit my remarks to a selection of communications, published up to the present time, which relate to his work.

It is with great hesitation that I refer frequently in this lecture to the work which my associates and I have done over the years in an effort to clarify certain problems, which Fåhræus has dealt with in his research studies. I believe, it is commensurate with the scientific spirit, to which we all ascribe including, of course, Robin Fåhræus, that the ultimate goal in any scientific endeavor is to serve the advancement of knowledge. On one point, I had to differ with Fåhræus in the discussion of the communication he presented in 1958. Certain new observations we made differed

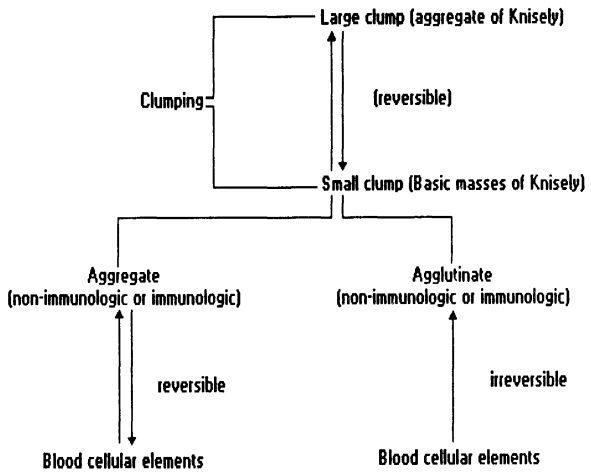

FIG. 1. Copley's concept on intravascular blood cellular clumping and Knisely's 'blood sludge'.

from those made by Fåhræus (57,60). These observations, which will be dealt with later (Section 3.61), concern clumps other than rouleaux, the so-called 'conglomerate erythrocyte clumps'. I hasten to say that when I talked with him following this public discussion, Fåhræus impressed me in saying that the facts, which I presented, were hitherto unknown to him. It was actually this exchange of views I had with him during the Congress which led to our friendship.

3.61 Erythrocyte Clumping - Rouleaux, Conglomerate Clumps and Knisely's 'Blood Sludge' in Health and Disease

In 1952, I redefined 'aggregation' to mean a reversible process and 'agglutination' an irreversible one (61). This differentiation eliminates the confusion, often found in the literature where these two terms are used interchangeably. This usage contributed greatly to the confusion, which continues to exist in the literature. Furthermore, I proposed the word 'clumping' as a noncommittal, general term for both reversible aggregation and irreversible agglutination (57,60).

Knisely introduced the unhappy term 'blood sludge' (52,57,60,62,63), which he considered a sign of disease. He categorically stated that what Fåhræus referred to as rouleau formation was synonymous with what he named 'blood sludge' (52). However, in 1958 I was surprised when Knisely mentioned to me, during his visit to my laboratory in London, he had lately noted that the erythrocytes, contained in blood sludges, were 'seen dispersed in the living circulation' (57,60).

Knisely claimed that the blood of healthy pregnant women as well as that of healthy horses does not contain erythrocyte

rouleaux and that the blood of pregnant women and from horses must have been, contrary to the assertion of Fåhræus, from diseased pregnant women and diseased horses (52). Knisely's claim, which was not based on sufficient evidence, was anathema to Robin Fåhræus.

Nevertheless, I tried to bring the views by Fåhræus and Knisely together, as shown in FIG. 1 (57,60).

Copley, Luchini and Whelan (62,63) observed both rouleau and non-rouleau erythrocyte clumps in blood samples from healthy human blood donors. The upper panel (a) of FIG. 2 shows a typical rouleau clump, while the lower panel (b) shows a second type of clump, which was mentioned above (62,63). It appears to be similar, if not identical, to Knisely's 'blood sludge', although the latter may still be a third type of erythrocyte clump.

Swank (62,63) found, following large butterfat meals in hamsters, similar erythrocyte clumps in the microcirculation of the

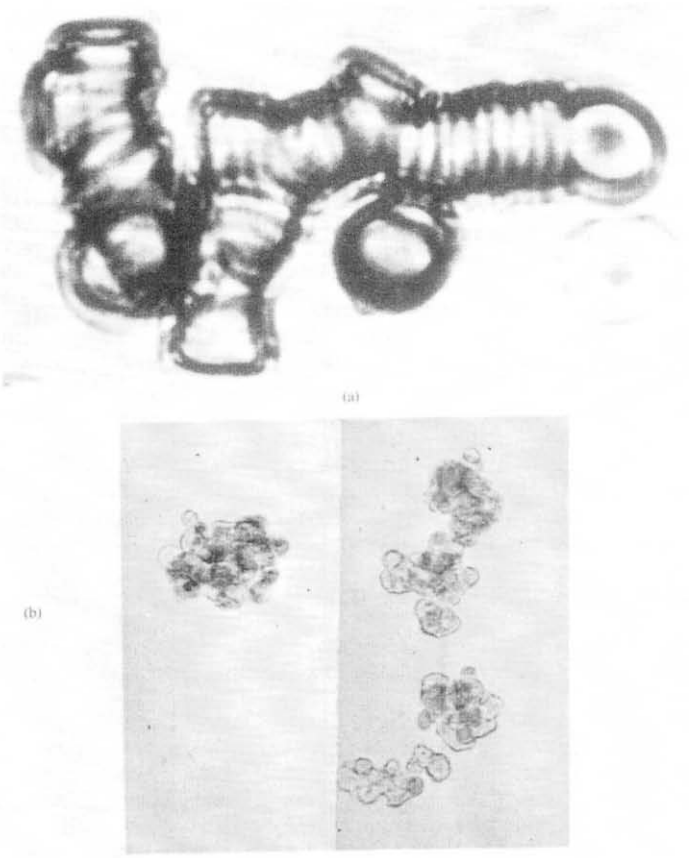

FIG. 2. (a) Typical erythrocyte rouleau; (b) Conglomerate erythrocyte clumps.

hamster's cheek pouch. He observed such irregular types of clumping in blood samples drawn from healthy dogs, rabbits and human subjects, in addition to rouleau formation. This type of irregular clumping was also observed by Swank following injection of high molecular weight dextran into animals (62,63).

In the discussion of Fåhræus' paper in 1958, I stated (57,60) the following: 'The question Dr. Knisely and numerous other authors posed in the literature is whether sludge formation, when it occurs, is a sign of disease. I certainly agree with Dr. Fåhræus that this is not necessarily so'. In this context, I made the following comment: 'Disease will only develop from such obstructions in the circulation, if they are numerous enough or if they are located in certain vital organs so that such impairments would develop to such a degree that clinical manifestations of marked pathologic changes become evident' (57,60).

3.62 Axial Stream of Erythrocytes in Glass Tubes and Blood Vessels

Of particular interest are the microscopic and photomicrographic measurements by Copley and Staple (37), referred to briefly in Section 3.41, of the vessel diameter and the width of the axial stream of erythrocytes in blood vessels of the hamster's cheek pouch. The velocity of blood flow was varied by an annular pneumatic cuff, through which the cheek pouch was passed. The width of the plasmatic zone was found to decrease gradually to zero as the cuff-pressure was raised and the velocity of blood flow progressively lowered. Our biomicroscopic measurements are in contrast to the assertion made by Vejlens (44) that the plasmatic zone has a constant width, which does not depend on the velocity of the flow of blood. Vejlens referred to observations by Thoma, Krogh and others (44) with regard to this claim. In 1955, Taylor (64) reported his studies on the flow of erythrocyte suspensions through glass capillaries, which do not support this assertion. It seems unlikely on more general rheological grounds discussed by Starkey (37,65,66). Our in vivo measurements support Taylor's extra vivum studies (37,64).

Fåhræus did not refer to the above mentioned claim made by Vejlens and earlier by Thoma, Krogh and others. This might have been due to the caution he exercised on statements not based on observations and/or actual measurements.

3.63 Fibrinogen-Fibrin Complexes and Erythrocyte Rouleau Formation

The involvement of fibrinogen in erythrocyte aggregation can also occur in a way which differs from that established by Fåhræus.

The initial fibrin formation by the action of thrombin on fibrinogen terminates either in a coagulum or, in a collateral pathway, in fibrin monomers which can form soluble, high molecular weight complexes with fibrinogen, the so-called 'fibrinogen-fibrin complexes'. These complexes are reversible and do not lead to a coagulum. Since thrombin in minute amounts is constantly being formed or activated in the circulation, fibrinogen-fibrin complexes are physiologically present and are continuously generated in the circulating blood. We, therefore, studied their role on the

suspension-stability and flow properties of blood systems.

In 1966, Copley et al reported that fibrinogen-fibrin complexes affected both the suspension-stability and the rheology of systems consisting of erythrocytes, suspended in plasma or in solutions containing purified fibrinogen (62,63). We found an increase in the extrapolated yield shear stress and an increased viscosity, accompanied by a decreased suspension-stability.

3.64 Fåhræus Effect

Several investigators studied quantitatively the 'Fåhræus Effect'. Barbee and Cokelet (49) found the relative tube hematocrit to be independent of the blood flow rate, the protein content of the continuous phase of the erythrocyte suspension and the stirring rate in the reservoir. Their results agree with those by Fåhræus (49).

Cokelet reported (67) that in capillaries, significantly smaller than hitherto used, the hematocrit of the blood leaving the glass capillary can be considerably lower than that in the feed reservoir. He called this effect, presumably due to a reduction in the number of erythrocytes entering the capillary orifice, the 'screening effect'. It was also shown that this cell screening was markedly affected by changes of capillary flow rate.

The experimental studies by Fåhræus and his evaluation (39,46) were exclusively aimed at the flow conditions within the capillary tube, thereby excluding effects which occur at the tube entrance, as was pointed out by Gaehtgens et al (68). These authors, therefore, considered the term 'Fåhræus effect' to be limited to what they referred to as the 'dynamic hematocrit reduction within the capillary'. Gaehtgens et al therefore investigated the effect of variations of flow rate on both the 'Fåhræus effect' and the 'screening effect'. They showed that variation of flow rate resulted in significant changes of the 'screening effect' and of the 'Fåhræus effect'. Upon reduction of volume flow rate, the cell screening increased, while the 'Fåhræus effect' decreased. A combined effect of both mechanisms was found by them to result in an increase of capillary hematocrit with decreasing flow rate. They concluded that increased velocity of the erythrocytes increases with shear stress due to shear dependent axial concentration of flowing erythrocytes.

In another communication, Gaehtgens et al (69) studied the effect of dextran-induced rouleau formation of human blood in glass capillaries with internal diameters from 15-95 μm. They noted the flow dependence of cell screening to be intensified, when compared to results obtained without dextran. Furthermore, the 'Fåhræus effect' indicated more pronounced dynamic hematocrit reduction within the glass capillary.

3.65 Erythrocyte Sedimentation at Various Shear Rates

The erythrocyte sedimentation of human blood at varying shear rates was studied by Copley, King and Huang (70) with the use of a special Couette type geometry, adapted to the Weissenberg

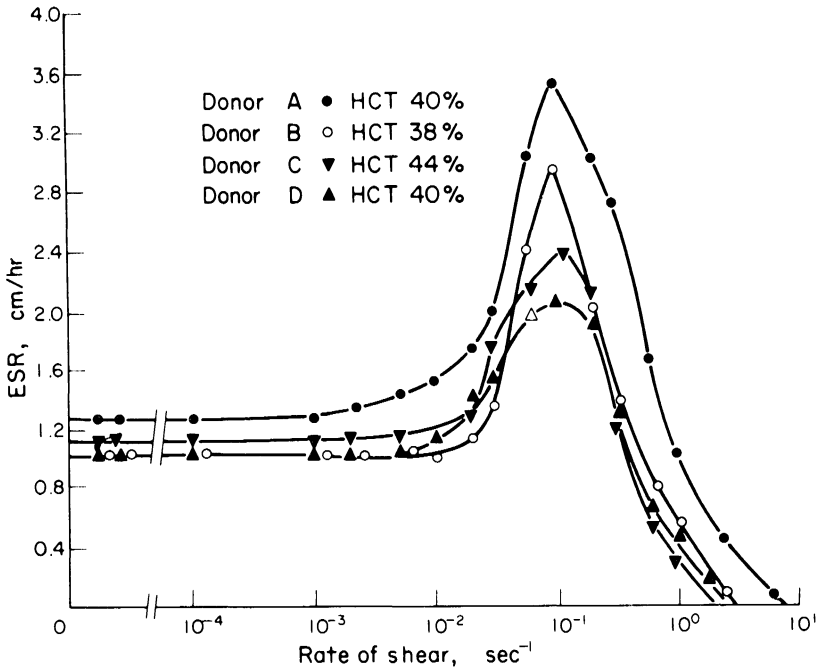

FIG. 3. Plots of erythrocyte sedimentation rate (ESR) vs. the rate of shear of blood from healthy human donors (A,B,C and D).

Rheogoniometer. As shown in FIG. 3, the erythrocyte sedimentation rates (ESR) were measured at various rates of shear from 0.0001 (10^{-4}) s^{-1} with readings taken at zero shear as control. No change in the sedimentation rate was found up to 0.01 s^{-1}. However, the sedimentation rate increased from 0.01 s^{-1}, reaching a maximum at 0.1 s^{-1}. From 0.1-10 s^{-1} the rate decreased progressively to zero. Individual differences found between donors were not significant. We gave tentative explanations for these findings in relation to the various shear rates, and discussed the balance and relationships between electrostatic forces and the diffusivity. Our findings may mirror flow properties in certain parts of the microcirculation, since erythrocyte sedimentation changes with varying shear rates. We reemphasized what Fåhræus had contended that increased erythrocyte sedimentation is not a sign of disease, but a normal occurrence in certain parts of the circulation, which may well be one of the prerequisites for maintaining certain physiological functions of the blood.

In an Appendix to the above reported findings, Oka (70) gave a mathematical interpretation of the parameters affecting erythrocyte sedimentation. He concluded from his theoretical considerations that aggregation and desaggregation will depend upon the electrostatic repulsion and the van der Waals attraction between the erythrocytes. Oka emphasized that in his mathematical treatment he assumed the erythrocytes as well as the aggregates to

be spherical in shape, which he emphasized is not the case. As it was well known to Oka, the erythrocyte is a biconcave disc and the aggregates form rouleaux of even more complex structures. He, therefore, emphasized that his equation for the frictional constant for such an anisodimensional structure will have to be replaced by another formula which needs to be developed, although he asserts that his simplified mathematical treatment may manifest the general features of the problem.

3.66 Viscoelastic Behavior of Blood and Erythrocyte Suspensions

Lessner, Zahavi, Silberberg, Frei and Dreyfus (71) were the first to have demonstrated the frequency dependent viscoelastic bahavior of whole blood. They attributed it to the rouleau network, but as Silberberg stated recently, membrane viscoelasticity contributes to this effect as well (72). No discernible difference was found by these authors between blood from healthy subjects and patients, as the scatter was too broad. Silberberg and his group found later that, when blood, secured from healthy volunteers served as its own control, was traumatized both mechanically and biochemically, 'the elastic modulus increased by 50 and 30 percent in the two cases respectively'. However, 'blood viscosity remained unchanged' (72). Thus, dynamic elasticity, according to these unpublished results, can serve as 'a sensitive indicator of changes in the subject's condition'(72).

Thurston concluded from his studies on the viscoelasticity of blood that 'in the description of oscillatory flow of blood in tubes, it is necessary that the blood be treated as a viscoelastic fluid and the appropriate tube flow relations be utilized' (73). He considered that relations which are based on the assumption that blood is a viscous fluid are not strictly applicable to blood (73). A subsequent publication dealt with the elastic effects in pulsatile blood flow (74). Thurston reasoned that if the shearing stress is large enough to break the erythrocyte aggregates, the flow may then become augmented. He found this description to be consistent with the findings by Copley, Huang and King (75) and Huang et al (76) to describe the rheology of blood at low shear rates. Thurston concluded that 'the stress at which the aggregates break is a fairly precise quantity and may be considered a basic property of blood' (74). Among his other conclusions, the following is cited: 'The elastic structure responsible for the pronounced viscoelasticity of blood may be large aggregates of erythrocytes. As the aggregation tendency is increased in pathological conditions, so then might the viscoelasticity become more pronounced' (74).

Chien et al (77) characterized the viscoelastic behavior of blood and erythrocyte suspensions over wide ranges of cell concentrations and frequencies of oscillation. They correlated these macrorheological findings with the microrheological findings observed microscopically by Copley et al (78) and, subsequently, microcinephotographically by Usami et al (79). Our findings indicate that at high hematocrits, up to 95 per cent, the viscoelastic behavior of erythrocytes in plasma and in a Ringer-albumin solution is essentially the same and the elastic component value gives an indication of the elastic modulus of the

cells presumably that of the cell membrane. At the lower hematocrits, for instance at 45 per cent, the monodispersed suspension of erythrocytes in Ringer-albumin solution shows a rather low elastic component value.

Goldsmith (80) reported in 1971 the deformation of erythrocytes and rouleaux in volume concentrations above 30 per cent in plasma at shear rates as low as 0.07 dyne cm^{-2}. He considered this effect to be due to crowding of the erythrocytes. In 1975, Chien et al (77) found a six-fold increase in the elastic component value of erythrocytes in plasma, most likely representing the elastic behavior of the rouleaux, as reported by Goldsmith (80). At low frequencies of oscillation, e.g., 0.01 Hz, suspensions of 45 per cent erythrocytes in plasma showed extensive rouleau formation with time and these large rouleaux exhibited cyclic elastic distortion at the imposed frequency. Our rheogoniometric studies at these low frequencies exhibited a considerable elastic component, as indicated in the elastic component value. The findings with 45 per cent erythrocyte suspensions are supported by our microrheological observations, mentioned above.

The results of the just mentioned oscillatory tests, all of which cannot be given here, have confirmed and extended the findings by Lessner et al (71) and Thurston (73,74). They support Thurston's concept that the elastic component of the rheological behavior of blood from healthy human subjects stems from the storage and dissipation of energy due to the elastic distortion of erythrocyte aggregates (74). Chien et al found that the elastic component of the rheological behavior of very concentrated erythrocyte suspensions reflects largely the elastic contribution from the deformation of single erythrocytes (77).

3.67 On Synergistic Effects of the Fåhræus-Lindqvist and Copley-Scott Blair Phenomena

The apparent viscosity of blood is not merely dependent upon the diameter of a capillary vessel, but as well on the nature of the surface of the capillary tube with which blood comes into direct contact. In 1958, studies of the viscosity of blood were made by me both in glass capillaries and, in comparison, in capillaries coated with fibrin or so-called 'fibrinized' (81). Marked decrease in apparent viscosity was found in the fibrinized capillaries. These studies were made on the basis of my concept that the endothelial cells, facing the flow of blood in the living microcirculation, have a lining of fibrin and/or fibrinogenin (40,41). Many studies by Copley, Scott Blair et al corroborated my original findings. Oka named this the 'Copley-Scott Blair phenomenon' (41,82). The 'Fåhræus-Lindqvist' and 'Copley-Scott Blair' phenomena behave complementarily in reducing markedly the apparent viscosity of blood in the microcirculation. They thus may aid, concomitantly and cumulatively, the action of the heart. This cumulative action might be demonstrated experimentally in glass and fibrinized capillary tubes of very small diameter. Such an experimental study has not yet been attempted.

The concept of the so-called endoendothelial fibrin and/or

fibrinogenin lining (EEFL), covering the endothelial cells, was first proposed by Copley in 1953, developed ever since, and more recently into a theory (40,41). Fibrinogenin is a new term which denotes the clotting of fibrinogen without the action of thrombin. The occurrence of fibrinogenin, studied by several investigators extra vivum during the past few decades, is now well established as another form of the clotting of fibrinogen. It can occur either by the action of factor XIII, as reported in several publications by Birger Blombäck et al (40,41,83), and, as found by Copley and King, in surface hemorheological studies without the action of factor XIII (83).

Fibrin and/or fibrinogenin are considered by me not merely to constitute the EEFL, but to be a main constituent of the so-called 'interendothelial cement substance', binding the endothelial cells, and surrounding them. Furthermore, fibrin(ogenin) is contained also in the vascular basement membrane. The EEFL is considered by me to be the main filtration barrier and not the endothelial cell, as it is generally believed. I cannot go into further detail of this concept or present here the experimental evidence thus far available. However, I consider it important to draw the attention to many publications, which deal with the EEFL and its significance in circulatory physiology and pathology (40,41).

The new developments pertaining to the roles of fibrin and fibrinogenin, both extra vivum and in vivo, could not have been known to Fåhræus. However, the central role which fibrinogen plays both in physiology and pathophysiology was emphasized by him prior to today's state of knowledge regarding fibrinogen.

3.68 Compaction Stasis of Erythrocytes in Inflammation

Copley and King (84) reported last January in Paris findings of normal stress versus rate of shear of hematocrits from 60 to 96 per cent. We found that 'with increasing shear rate and hematocrit, the value of normal stress increases proportionally to the increasing shear stress, and reflects the increasing elongation of the erythrocytes in the direction of flow'. It is difficult to interpret these extra vivum findings in relation to the in vivo situation. However, we inferred from these findings that it may be possible that, in certain conditions, normal stress related to high hematocrit may occur in vivo within the affected vessel segment and result in increased vascular permeability.

Erythrocyte aggregation or rouleau formation should not be merely related to the blood, but also to the vessel wall. It can lead to increased capillary or vascular permeability concommitant with the compaction of erythrocyte aggregates in the vessel lumen, a phenomenon which I named 'compaction stasis' (85). The first in vivo observations on erythrocyte aggregation and desaggregation, which van Lewenhoek (or Leeuwenhoek, as his name is usually spelled) sent in a letter to the Royal Society in 1699 (86,87), appear to be already related to 'compaction stasis'. Fåhræus referred also to observations by van Leeuwenhoek of erythrocytes in glass tubes, in which the aggregation of erythrocytes is described. According to Fåhræus, van Leeuwenhoek found the clumping of erythrocytes in normal blood in such a way that their

borders were no longer visible (11).

The term 'Cohnheim Compaction Phenomenon', introduced in 1985, refers to observations reported in 1882 by Julius Cohnheim on reversible erythrocyte clumps, occurring in inflammation (8,84,88). Time does not permit me to go into further detail regarding our rheological findings on erythrocyte rouleaux at hematocrits up to 96 per cent, which we reported this year in Paris. We referred to the 'Cohnheim compaction phenomenon' of increased focal capillary or vascular permeability, not suspected hitherto in conditions such as polycythemia, circulatory shock and mountain sickness (84).

What I mentioned above gives, in my appraisal, new evidence for the fertility of the findings by Robin Fåhræus in its significance for present-day clinical hemorheology.

The pioneering thoughts of Robin Fåhræus serve as the guiding spirit in studies on erythrocyte aggregation and desaggregation, which continue to have a great impact in current hemorheological studies.

The aggregation and desaggregation of erythrocytes were dealt with in several communications at a conference on surface hemorheology, held in 1982 at the New York Academy of Sciences (89). In his Fåhræus Award Lecture, Stoltz (90) emphasized that 'erythrocyte aggregation energy' is produced by the formation of intercellular macromolecular bridges and 'desaggregation energy' is the result of electrostatic repulsion between the adjacent cell surfaces, when the erythrocytes move very close together. Stoltz stated that '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 RBC membrane curvature during aggregation' (90). He concluded that in the presence of shear stress, the erythrocytes tend to desaggregate due to the effect of the mechanical shear. Stoltz, therefore, considered the net aggregation energy between adjacent erythocytes to depend on several types of energy to which he referred (90).

The guiding spirit of Robin Fåhræus is likewise mirrored in conferences entirely devoted to erythrocyte aggregation, which were organized by J.F. Stoltz. They were first held in Geneva, Switzerland in 1986 and this year in Paris. Their Proceedings were published in CLINICAL HEMORHEOLOGY, as well as in separate books in French (84,87). The next Conference may be held in Reykjavik in September 1990.

Sessions on erythrocyte aggregation have been part of the International Congresses of Biorheology. The 7. International Congress will be held in Nancy, France from 18-23 June, 1989. The 8. International Congress of Biorheology will probably be held in the People's Republic of China in 1992. Sessions on erythrocyte aggregation have been organized as parts of the European Conferences on Clinical Hemorheology. The next one will be at Frankfurt, FRG, from 14-17 June, 1989, just prior to the International Congress.

3.7 The Fåhræus Paradox

The findings by Fåhræus in glass capillaries that erythrocyte rouleaux facilitate the flow of blood and his considerations that, if these rouleaux are markedly increased, they can block vessels in the circulation and cause thrombosis and/or thromboembolization (12,43), have led me to the following postulation. These dual roles of erythrocyte rouleaux can thus have in vivo either beneficial or deleterious effects on the health of the affected subject. Although, to my knowledge, Fåhræus did not elaborate on these two antagonistic actions, he certainly drew my attention to them. I am, therefore, proposing to call these paradoxic occurrences the 'Fåhræus Paradox'. It seems to me that this so-called 'Fåhræus Paradox' can favor a biological process or bring about an occurrence in vivo which can change to its opposite and possibly also vice versa.

From my own activities, I like to mention the following examples of the 'Fåhræus Paradox'. In the arrest of hemorrhage, the infliction of a vessel wound will lead to a thrombus, plugging the hole in the vessel wall and thus initiating hemostasis. However, the thrombus, to which I referred to as 'wound thrombus', may grow intravascularly and lead clinically to a thrombotic condition (91). Another example would be the above mentioned endoendothelial lining due to steady fibrin and/or fibrinogenin formation, which is controlled, as I see it, by steady fibrinolysis and/or fibrinogenolysis (40,41). A disturbance in these steady processes could lead to the obstruction of the affected vessel lumen and, by further growth of these gels of fibrin and/or fibrinogenin, initiate the clinical condition of thrombosis. In the latter case the 'Fåhræus Paradox' may be synonymous with a disturbance in homeostasis, but this may not necessarily be with regard to augmented rouleau formation or with the initiation of thrombosis following an injury to the vessel wall.

Many other examples of the 'Fåhræus Paradox' can probably be found in the biomedical sciences for application to the practice of different fields of medicine and surgery. Such examples may contribute to our awareness or understanding with regard to the development of pathological conditions or disease processes.

The increase of erythrocyte rouleaux in vivo by, for instance, the infusion of gelatin or other apparently innocuous agents, may introduce, therefore, risks inherent in the 'Fåhræus Paradox'.

The 'Fåhræus Paradox' may well be a general biomedical paradoxic occurrence, which, as I see it, needs further study by pathologists engaged in various fields.

4. HIS ROLE IN THE ORGANIZATION OF BIORHEOLOGY

Robin Fåhræus was a pioneer in experimental and clinical hemorheology long before biorheology with its different fields became an organized science. He played also an important role in its organization. Robin Fåhræus, George William Scott Blair, myself and other participants of the 3. International Congress on Rheology formed a committee to investigate the possibilities of

Dedicated to

PROFESSOR ROBIN FÅHRAEUS

Pioneer and Nestor of Contemporary Hemorheology

FIG. 4

initiating an International Society of Biorheology (1). The foundation of such a Society, however, was considered by us subsequently to be premature. Since the initiation of the new journal BIORHEOLOGY in 1959 by Robert Maxwell, President of Pergamon Press, in London, Robin Fåhræus was one of its Editors (92).

In 1963, Fåhraeus participated in the 'Symposium on Biorheology', held on four days as part of the 4. International Congress on Rheology at Brown University in Providence, RI, USA, as mentioned in Section 2 (6,7).

The Proceedings of the Symposium on Biorheology were published as part 4 of those of the entire Congress. The frontispiece of this volume has a portrait photograph of Robin Fåhræus to whom it was dedicated, (FIG. 4). The epithet 'Pioneer and Nestor of Contemporary Hemorheology' was placed in the dedication below his

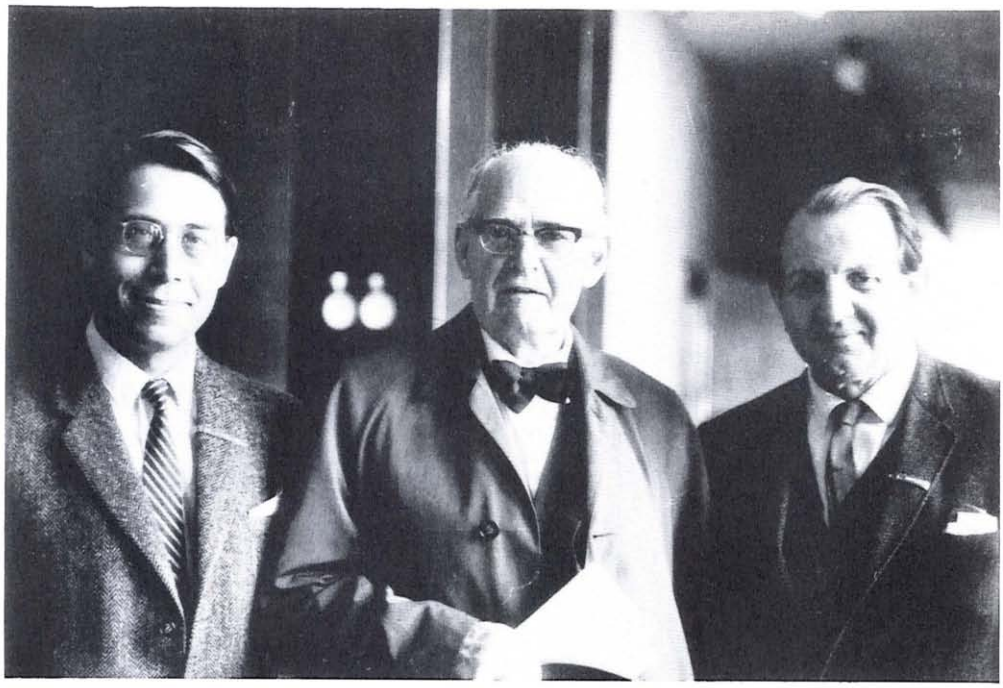

FIG. 5. Robin Fåhræus with George Bugliarello (left), Secretary-General (at present President of Polytechnic University, New York) and Alfred L. Copley (right), President of the newly founded Society and of the Conference at the University of Iceland. The photo was taken in Reykjavik on 11 July 1966.

name. During my Opening Address of the Symposium, when this dedication was announced, the Symposium participants gave a standing ovation to Robin Fåhræus, who accepted this honor (93).

The last international meeting in which Robin Fåhræus participated (FIG. 5) was the 1. International Conference on Hemorheology, held in 1966 at the University of Iceland in Reykjavik, where the International Society of Hemorheology was founded (62). During this Conference Robin Fåhræus was honored (FIG. 6) by the newly founded International Society of Hemorheology in becoming the first Awardee (FIG. 7) of the Poiseuille Gold Medal (94,95).

The citation on the backside of the Poiseuille Gold Medal reads: 'To Robin Fåhræus, Nestor of Hemorheology, For His Pioneering Research, Presented at First International Conference on Hemorheology, University of Iceland, 10-16 July, 1966, Reykjavik. The International Society of Hemorheology.'

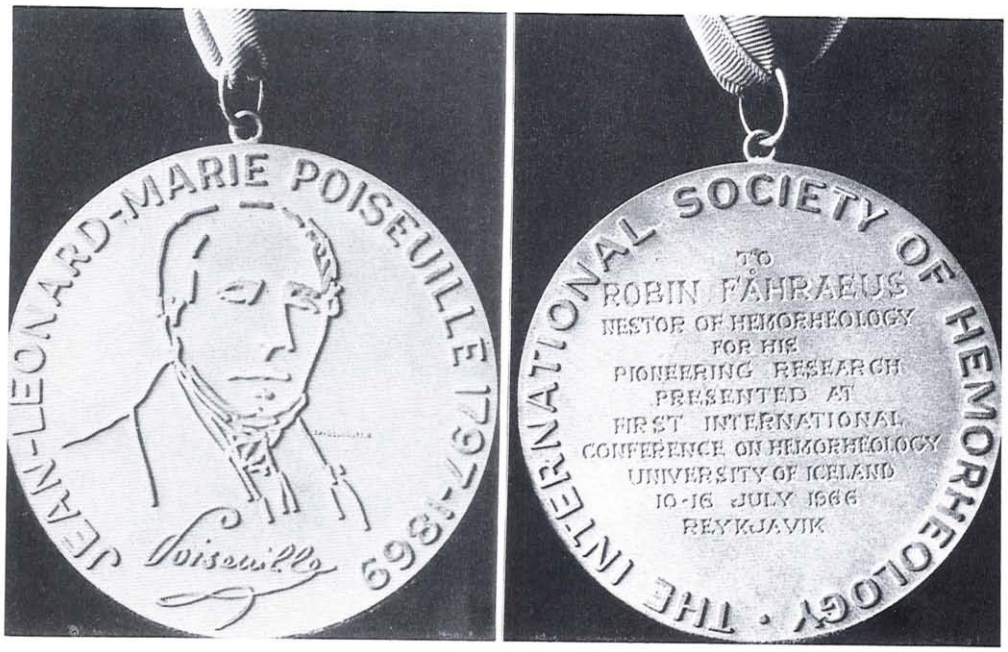

FIG. 6. The Poiseuille Gold Medal awarded by the International Society of Hemorheology to Robin Fåhræus, its first recipient, at the University of Iceland, Reykjavik in 1966. Left panel: The medal's front side was designed by the Icelandic artist Nina Tryggvadottir. It has a replica of the signature of Poiseuille. Right panel: Back side with citation.

Following Robin Fåhræus, the recipients of the Poiseuille Gold Medal Award were George W. Scott Blair (UK) in Heidelberg, 1969; Alfred L. Copley (USA) in Lyon, 1972; Syoten Oka (Japan) in Rehovot, 1975; Maurice Joly (France) in La Jolla, 1978; Alex Silberberg (Israel) in Tokyo, 1981; Hellmut Hartert (F.R. Germany) in Baden-Baden, 1983; and Yuan-Cheng (Bert) Fung (USA) in Vancouver, 1986.

It should be noted that, in 1969, the scope of the Society was expanded to include all fields of biorheology and the Society was thus renamed the International Society of Biorheology. Soon after, it became 'An Affiliated Commission of the Union of Pure and

FIG. 7. Robin Fåhræus bearing the Poiseuille Gold Medal. Reykjavik, 15 July 1966.

Applied Biophysics'.

The pioneering studies by Robin Fåhræus were also recognized by the European Conference on Clinical Hemorheology, held under the auspices of the Royal Society of Medicine, London in 1981 by the newly established Robin Fåhræus Medal Award. Every two years since, when the European Conference convenes, this Award has been bestowed to a leading clinical hemorheologist. The Robin Fåhræus Medal Awardees were Shu Chien (USA) in London, 1981; John A. Dormandy (UK) in Baden-Baden, 1983; Holger Schmid-Schönbein (F.R. Germany) in Siena, 1985; and Jean-François Stoltz (France) in Bordeaux, 1987.

5. THE PERSON

Sourander and Breimer recently provided a brief biography of Robin Fåhræus (3). They gave a vivid picture of him as an enthusiastic lecturer and a popular orator, cherished by many generations of students and colleagues. Robin Fåhræus mentioned to me at one time that he liked to paint, however I learned recently (3), that he was an accomplished artist. This is

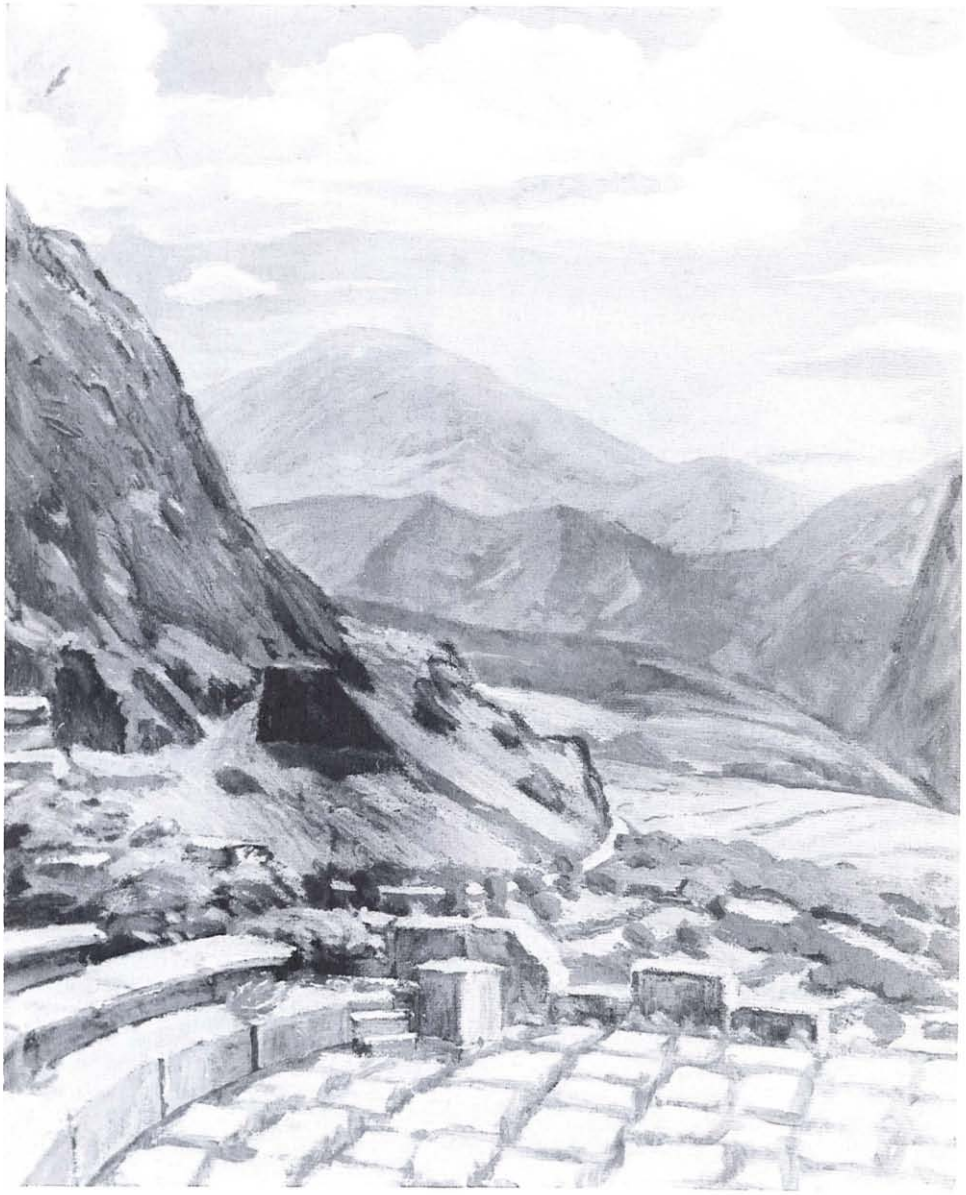

FIG. 8. Painting, oil on canvas, 43 x 36 cm, about 1950, Delphi, Greece. Collection: Klas Fåhræus, Djursholm, Sweden. The painting shows a view of the theater and its surroundings at Delphi, Greece. In the foreground are the ruins of the theater, next to those of the temple of Apollo. Klas Fåhræus, architect and painter, made in a letter of 13 January to the author the following comments as related to the painting: 'My father has placed himself in the ruins of the old theater and caught the view of the valley. He worshipped everything combined with ancient Greece, so he must have been very pleased. I think he went there several times after the war'.

manifested in his many paintings (FIG. 8), including landscapes from the West coast of Sweden, where he spent his summer vacations, and in several self-portraits. I had not known that Robin was the son of Klas Fåhræus, who was a well-known author, art critic and collector. Robin's mother was Olga Björkegren, the most prominent Swedish dramatic actress of her time (FIG. 9). Sourander and Breimer pointed out that Fåhræus grew up in a highly cultured environment, the family home being a literary and artistic center in Stockholm at the turn of the century.

FIG. 9. Photo of Olga Björkegren Fåhraeus with her son Robin.

I was glad to learn that Robin Fåhræus felt a strong affinity for Claude Bernard, both as a medical scientist and as a person. As he shared Claude Bernard's involvement in the plastic arts, he might have also known that several biomedical scientists, such as Louis Pasteur, who was a highly accomplished painter, Frederick Grant Banting (1891-1941) and Charles Herbert Best (1899-) also enjoyed being painters.

Many participants of the 'Symposium on Biorheology' (6), held in 1963, in Providence, USA, will remember the reaction by Fåhræus,

FIG. 10. The Fåhræus Medal, cast in silver, is awarded every two years to a clinical hemorheologist by the European Conference on Clinical Hemorheology. Both sides of the Medal were designed by L. Alcopley. Upper panel: The medal's front side shows a portrait of Robin Fåhræus. Surrounding the portrait is the name of the Awardee with the place and year of the Conference. (As shown, in 1983 the Medal was presented to John Dormandy in Baden-Baden). Lower panel: Backside of the Fåhræus Medal.

when I announced that the Symposium volume will be dedicated to him (Sections 2 and 4). He got up and in his excitement exclaimed extemporaneously: 'No, no. I cannot believe it. What will my wife say!' (8). This episode of his spontaneous reaction to honoring him may give an insight into Robin Fåhræus as a person. It seems to be also reflected in his anger against Knisely who thoughtlessly questioned his integrity.

During the few meetings I had with Robin Fåhræus in different countries, I sensed in him a person with great warmth, kindness and with an incisive mind. Although I only knew him as a person during the last decade of his life, he struck me as a non-pretentious man, well aware of his attainments in science, in its history and importance for humanity. He carried a natural dignity with humor and wit. Although he must have been aware of the meaningfulness of his contributions to society, he was refreshing in his modesty.

It pleased me very much when the organizers of the European Conference of Clinical Haemorheology asked me to design, in my other activity as an artist under the name (Mr.) L. Alcopley, the two sides of the medal. In drawing the portrait of Robin Fåhræus (96,97), I was guided by the photographic portrait which Mrs. Fåhræus selected for the frontispiece, mentioned in Sections 2 and 4. I made this portrait as a line drawing to appear on the medal in an elevation of the lines of the drawing, shown in FIG. 10.

From an account about the Medal's front side, which bears the portrait of Robin Fåhræus, I should like to cite: 'No photographic likeness was intended, but nevertheless a likeness of his head with his clear and far-sighted way of looking, his somewhat critical attitude which is also somehow expressed in his sensuous lips and bob of the nose, which was, as compared to the large head, rather small. The rectangular lower part of his face is extended in a more dome-like or egg-shaped part of his forehead and skull...All in all, I wanted to portray my late friend Robin Fåhræus as a strong personality and the way I saw him. When I knew him, he was much older than at the time he was photographed for the portrait which I used to start with. Artistically the line drawing is a portrait by Alcopley and, in this way, would differ from any rendering by other artists' (96). The backside of the Fåhræus Medal suggests, in the center, the shape of the heart. It is surrounded by continuous parallel curved lines, symbolizing the circulation. The drawing likewise suggests the erythrocyte and its deformability (97).

6. CONCLUDING REMARKS

Robin Fåhræus has written his scientific communications lucidly and candidly. As an author he serves as a fine example in his published research studies. Reading his accounts pertaining to the unique history of medicine is sheer pleasure. We need to examine the contemplative nature of some of his writings as antidotes to the prevailing custom in taking for granted the history of ancient thoughts and earlier findings in medicine and science in general. As a biomedical scientist, Robin Fåhræus gave his undivided attention to his scientific communications, and a clear presentation.

In the pursuit of any field of science, it appears necessary to introduce occasionally a jump to provide the basis for a new vision. This in itself is the creative process which scientists share with those engaged in other activities of the mind. In this sense, Robin Fåhræus was a creator.

AKNOWLEDGEMENT

The Author thanks Professor Patrick Sourander, University of Göteborg School of Medicine, who is completing a biography of Robin Fåhræus, for kindly providing certain information for this lecture.

7. REFERENCES

1. COPLEY, A.L. The 100th birthday of Robin Fåhræus. In: Robin Fåhræus Memorial Issue, Biorheology 25, 823-825, 833-834, 1988; Thrombosis Research 52, 495-497, 505-506, 1988; Clinical Hemorheology 8, 821-823, 831-832, 1988.

2. FÅHRÆUS, R. Läkekonstens historia (History of Medicine), 3 volumes. Stockholm: Albert Bonniers Förlag, 1946-1950.

3. SOURANDER, P. and BREIMER, L.H. Robin Fåhræus (1888-1968). In: Robin Fåhræus Memorial Issue, Biorheology 25, 827-832, 1988; Clinical Hemorheology 8, 825-830, 1988; Thrombosis Research 54, 499-504, 1988.

4. FÅHRÆUS, R. Till 250 - års minnet av Linnés födelse (The 250th Anniversary of Linnæus' Birth). Nordisk Medicin 57, 731-760, 1957.

5. SOURANDER, P. Robin Fåhræus som medicinhistoriker. Till 100-årsminnet av hans födelse. Nordisk Med. Historisk Årsbok, 1988, in press.

6. COPLEY, A.L. (Ed.) Symposium on Biorheology. Proceedings of the 4. International Congress on Rheology, Brown University, Providence, RI, USA, 26-30 August 1963, Part 4. New York-London: Interscience Publ. - John Wiley & Sons, 1965, 645 pp.

7. FÅHRÆUS, R. Archaic Hemorheology. The Early Historical Significance of Blood Sedimentation. In: A.L. Copley, Ed., (6), pp. 11-17.

8. COPLEY, A.L. The history of clinical hemorheology. Clinical Hemorheology 5, 765-812, 1985; 6, 165, 1986; The History of Clinical Hemorheology. Bordeaux, 5. European Conference on Clinical Hemorheology, 29 June - 1 July, 1987 (Reprinted by the Conference).

9. FÅHRÆUS, R. Die erhöhte Senkungsgeschwindigkeit der roten Blutkörperchen und ihre Bedeutung für die antike Humoralpathologie. Bull. Schweiz. Akad. Med. Wiss. 3, 67-80, 1947/48.

10. FÅHRÆUS, R. Rheology in the history of medicine. Laboratory

Practice (London) 15, 44-47, 52, 1966.

11. FÅHRÆUS, R. Die Grundlagen der neueren Humoralpathologie. Virchows Arch. path. Anat. 333, 176-189, 1960.

12. FÅHRÆUS, R. The Suspension-Stability of the Blood. Stockholm: P.A. Norstedt & Söner, 1921, 228 pp.

13. SVEDBERG, T. and FÅHRAEUS, R. A new method for the determination of the molecular weight of proteins. J. Am. Chem. Soc. 48, 430-439, 1926.

14. FÅHRÆUS, R. Glycogen formation in surviving liver tissue. Acta Soc. Med. Upsaliensis 56, 92-102, 1956.

15. FÅHRÆUS, R. The optimum temperature of the acid phosphatases of the erythrocyte. Acta Soc. Med. Upsaliensis 53, 321-330, 1953.

16. COPLEY, A.L. Rheological problems in biology. In: J.M. Burgers et al (Eds.) Proc. Internat. Congr. on Rheology, Holland, 1948. Amsterdam: North-Holland Publ. Co., 1949, I/47-I/61; III/8-III/11.

17. COPLEY, A.L. The future of the science of biorheology. Biorheology 19, 47-69, 1982.

18. SILBERBERG, A. and COPLEY, A.L. On the scope of the science of biorheology and the aims of BIORHEOLOGY. Biorheology 23, 307-309, 1986.

19. COPLEY, A.L. The endoendothelial fibrin film and fibrinolysis. In: Proc. VIII. Cong. Hematol., Tokyo, 1960. Vol. 3. Tokyo: Pan-Pacific Press, 1962, pp. 1648-1666.

20. COPLEY, A.L. Perihemorheology rather than parahemorheology. Biorheology 24, 285-286, 1987; Clinical Hemorheology 7, 377-378, 1987.

21. VIRCHOW, R. Arch. Pathol. Anat. u. Physiol. (Virchow's Archiv) 1, 547- , 1847; Gesammelte Abhandlungen zur wissenschaftlichen Medizin. Frankfurt a.M.: Meidinger Sohn & Co., 1856.

22. DENIS, P. Mémoire sur le sang. Paris: J.B. Baillière et fils, 1859.

23. HAMMARSTEN, O. Undersökningar af de s.k. fibringeneratorerna fibrinet samt fibrinogenet koagulation. Upsala Läkareförens. Förh. 11, 538-579, 1876.

24. HAMMARSTEN, O. Ueber das Fibrinogen. Pflüger's Arch. ges. Physiol. 19, 563- , 1879; 22, 431- , 1880.

25. BLOMBÄCK, B. Studies on fibrinogen: Its purification and conversion into fibrin. Acta Physiol. Scand. 43, Suppl. 148, 1-51, 1958.

26. ARTHUS, M. and PAGES, C. Nouvelle théorie chimique de la coagulation du sang. Arch. Physiol. Norm. Path. 22, 739- , 1890.

27. DINTENFASS, L. Blood Viscosity, Hyperviscosity, and Hyperviscosaemia. Lancaster-Boston-The Hague-Dordrecht: MITP Press Ltd., 1985, 482 pp.

28. CHIEN, S., DORMANDY, J., ERNST, E. and MATRAI, A. (Eds.) Clinical Hemorheology. Applications in Cardiovascular and Hematological Disease, Diabetes, Surgery and Gynecology. Dordrecht - Boston - Lancaster: Martinus Nijhoff Publ., 1987, 398 pp.

29. HARTMANN, A. and KUSCHINSKY, W. (Eds.) Cerebral Ischemia and Hemorheology. Berlin-Heidelberg-New York-Tokyo: Springer-Verlag, 1987, 552 pp.

30. EHRLY, A.M. Therapeutische Hämorheologie. Berlin-Heidelberg-New York-Tokyo: Springer-Verlag, 1989, 258 pp. (in press); Therapeutic Hemorheology. New York-Berlin-Heidelberg-Tokyo: Springer-Verlag, 1989 (in press).

31. HESS, W.R. Gehorcht das Blut dem allgemeinen Strömungsgesetz der Flüssigkeiten? Pflüger's Arch. Physiol. 164, 603-644, 1915.

32. COPLEY, A.L., KRCHMA, L.C. and WHITNEY, M.E. Humoral rheology. I. Viscosity studies and anomalous flow properties of human blood systems with heparin and other anticoagulants. J. Gen. Physiol. 26, 49-64, 1942.

33. POISEUILLE, J.L.M. Recherches expérimentales sur le mouvement des liquides de natures différents dans les tubes de très petits diamètres. Annales de Chimie et de Physiques, Troisième Série t.xxi, 1847.

34. SCOTT BLAIR, G.W. Some experimental methods for biorheologists. Laboratory Practice (London) 15, 48-52, 59, 1966.

35. DUNCAN, J.M.D. and GAMGEE, A. Notes of some experiments on the rate of flow of blood and some other liquids through tubes of narrow diameter. J. Anat. & Physiol. 5, 150-157, 1871.

36. POISEUILLE, J.L.M. Ann. des Sciences naturelles 2. Zoology 5, 111- , 1836. Cited by A.L. Copley et al (37).

37. COPLEY, A.L. and STAPLE, P.H. Haemorheological studies on the plasmatic zone in the microcirulation of the cheek pouch of Chinese and Syrian Hamsters. Biorheology 1, 3-14, 1962.

38. SCHKLAREWSKY, A. Ueber das Blut und die Suspensions-Flüssigkeiten. Pflüger's Archiv f. Physiol. 1, 603-644, 1868.

39. FÅHRÆUS, R. Die Strömungsverhältnisse und die Verteilung der Blutzellen im Gefässsystem. Zur Frage der Bedeutung der

intravasculären Erythrocytenaggregation. Klin. Wochenschr. 7, 100-106, 1928.

40. COPLEY, A.L. Endoendothelial fibrin(ogenin) lining: The interface between the two portions of the 'vessel-blood organ'. In: S. Seno, A.L. Copley, M.A. Venkatachalam, Y. Hamashima and T. Tsujii (Eds.) Glomerular Dysfunction and Biopathology of Vascular Wall. Satellite Symp. 3. Internat. Congr. on Cell Biology, Kurashiki, Japan, 1984. Tokyo-New York-London: Academic Press, 1985, pp. 59-86.

41. COPLEY, A.L. The endoendothelial fibrin(ogenin) lining and its physiological significance. Biorheology 25, 377-399, 1988.

42. FÅHRÆUS, R. Über die Ursachen der verminderten Suspensionsstabilität der Blutkörperchen während der Schwangerschaft (Vorläufige Mitteilung). Biochem. Zschr. 89, 355-364, 1918.

43. FÅHRÆUS, R. The influence of the rouleau formation of the erythrocytes on the rheology of the blood. Acta Med. Scand. 161, 151-165, 1958.

44. VEJLENS, G. The distribution of leukocytes in the vascular system. Acta Pathol. et Microbiol. Suppl. 33, 11-239, 1938.

45. JEFFERY, C.B. Proc. Royal Soc. London. Series A 102, 161-, 1922. Cited by R. Fåhræus (43).

46. FÅHRÆUS, R. The suspension stability of the blood. Physiol. Reviews 9, 241-274, 1929.

47. FÅHRÆUS, R. and LINDQVIST, T. The viscosity of the blood in narrow capillary tubes. American J. Physiol. 96, 562-568, 1931.

48. SCOTT BLAIR, G.W. The importance of the sigma phenomenon in the study of the flow of blood. Rheologica Acta 1, 123-126, 1958.

49. BARBEE, J.H. and COKELET, G.R. The Fåhræus effect. Microvasc. Res. 3, 6-16, 1971.

50. FÅHRÆUS, R. The erythrocytes-plasma interface and the consequence of its diminution. The Lancet, 16 September, 630-635, 1939.

51. KNISELY, M.H. Spleen studies. I. Microscopic observations of the circulatory system of living unstimulated mammalian spleens. Anat. Rec. 65, 23-50, 1936.

52. KNISELY, M.H. An annotated bibliography on sludged blood. Postgrad. Med. 10, 15-24; 80-93, 1951.

53. FÅHRÆUS, R. The influence of the spleen on normal and pathologic cells in the blood. Zeitschr. f. Krebsforschung 65, 560-564, 1963.

54. HAMMARSTEN, O. Lärobok i Fysiologisk Kemi, 1883, p. 141. Cited by R. Fåhræus (53).

55. HEILMEYER, L. Die hämolytische Hypersplenie. Dtsch. Arch. klin. Med. 179, 292- , 1936. Cited by R. Fåhræus (53).

56. BERGENHEM, B. and FÅHRÆUS, R. über spontane Hämolysinbildung im Blut, unter besonderer Berücksichtigung der Physiologie der Milz. Z. ges. exp. Med. 97, 555-587, 1936. Cited by R. Fåhræus (53).

57. FÅHRÆUS, R. Intravaskuläre Erythrozytenaggregation und ihre Einwirkung auf die Rheologie des Blutes. Rheologica Acta 1, 656-665, 1961.

58. FÅHRÆUS, R. Eclampsia - A disease of checked microcirculation. Acta Obst. et Gynec. Scandinav. 41, 101-114, 1962.

59. FÅHRÆUS, R. Acta Soc. Med. Upsal. 60, 77, 1960. Cited by R. Fåhræus (58).

60. COPLEY, A.L. On red blood cell (RBC) filterability, presented in 1958 by Robin Fåhræus, his controversy to Knisely's 'blood sludge' and Copley's concept on blood cellular clumping. Clinical Hemorheology 1, 219-225, 1981.

61. COPLEY, A.L. The rheology of blood. A survey. J. Colloid Science 7, 323-333, 1952.

62. COPLEY, A.L. (Ed.) Hemorheology. Proceedings of the First International Conference, The University of Iceland, Reykjavik, 10-16 July 1966. Oxford-London-New York: Pergamon Press, 1968, 869 pp.

63. COPLEY, A.L., LUCHINI, B.W. and WHELAN, E.W. On the role of fibrinogen-fibrin complexes in flow properties and suspension-stability of blood systems. In: A.L. Copley, Ed. (62), pp. 375-388.

64. TAYLOR, M. Austral. J. Exp. Biol. Med. Sci. 33, 1- , 1955. Cited by A.L. Copley and P.H. Staple (37).

65. STARKEY, T.V. Brit. J. appl. Phys. 6, 34- , 1955; 7, 52- , 1956. Cited by A.L. Copley and P.H. Staple (37).

66. STARKEY, T.V. Nature (London) 178, 207- , 1956. Cited by A.L. Copley and P.H. Staple (37).

67. COKELET, G.R. Macroscopic rheology and tube flow of human blood. In: Microcirculation Vol. 1. J. Grayson and W. Zingg (Eds.), New York: Plenum Publishing Co., 1976, pp. 9-31.

68. GAEHTGENS, P., ALBRECHT, K.H. and KREUTZ, F. Fåhræus effect and cell screening during tube flow of human blood. I. Effect of variation on flow rate. Biorheology 15, 147-154, 1978.

69. GAEHTGENS, P., ALBRECHT, K.H. and KREUTZ, F. Fåhræus effect

and cell screening during tube flow of human blood. II. Effect of variation on flow rate. Biorheology 15, 155-161, 1978.

70. COPLEY, A.L., KING, R.G., HUANG, C.-R. and OKA, S. Erythrocyte sedimentation of human blood at varying shear rates. Biorheology 13, 281-286, 1976.

71. LESSNER, A., ZAHAVI, J., SILBERBERG, A., FREI, E. and DREYFUS, F. The viscoelastic properties of whole blood. In: Theoretical and Clinical Hemorheology. Proc. 2. Internat. Conf., Internat. Soc. of Hemorheology, University of Heidelberg, Heidelberg, F.R. Germany, 27.7.-1.8. 1969. H.H. Hartert and A.L. Copley (Eds.) Berlin-Heidelberg-New York: Springer-Verlag, 1971, pp. 194-205.

72. SILBERBERG, A. Personal communication, 22 November 1988.

73. THURSTON, G.B. Frequency and shear rate dependence of viscoelasticity of human blood. Biorheology 10, 375-382, 1973.

74. THURSTON, G.B. Elastic effects in pulsatile blood flow. Microvasc. Res. 9, 145-157, 1975.

75. COPLEY, A.L., HUANG, C.R. and KING, R.G. Rheogoniometric studies of whole human blood at shear rates from 1000 to 0.0009 sec^{-1}. Part I - Experimental findings. Biorheology 10, 17-22, 1973.

76. HUANG, C.R., KING, R.G. and COPLEY, A.L. Rheogoniometric studies of whole human blood at shear rates down to 0.0009 sec^{-1}. Part II -Mathematical interpretation. Biorheology 10, 23-28, 1973.

77. CHIEN, S., KING, R.G., SKALAK, R. USAMI, S. and COPLEY, A.L. Viscoelastic properties of human blood and red cell suspensions. Biorheology 12, 341-346, 1975.

78. COPLEY, A.L., KING, R.G., CHIEN, S. USAMI, S., SKALAK, R. and HUANG, C.R. Microscopic observations of viscoelasticity of human blood in steady and oscillatory shear. Biorheology 12, 257-261, 1975.

79. USAMI, S., KING, R.G., CHIEN, S., SKALAK, R., HUANG, C.R. and COPLEY, A.L. Microcinephotographic studies on red cell aggregation in steady and oscillatory shear - A note. Biorheology 12, 323-325, 1975.

80. GOLDSMITH, H.L. Deformation of human red cells in tube flow. Biorheology 7, 235-242, 1971.

81. COPLEY, A.L. Adherence and viscosity of blood contacting foreign surfaces, and the plasmatic zone in blood circulation. Nature 181, 551-552, 1958.

82. OKA, S. Theoretical approach to the effect of wall surface condition in hemorheology. In: A.L. Copley, Ed. (62).

83. BLOMBÄCK, B., PROCYK, R., ADAMSON, L. and HESSEL, B. Factor XIII induced gelation of human fibrinogen, an alternative thiol enhanced, thrombin independent pathway. Thrombosis Research 37, 613-628, 1985.

84. COPLEY, A.L. and KING, R.G. Agrégation érythrocytaire, stase de compactage, phenomène de compactage de Cohnheim et inflammation. In: J.F. Stoltz (Ed.) Hémorhéologie et Agrégation Erythrocytaire. Applications Cliniques. 2. Symposium International. Paris, Janvier 1988. Paris: Editions Médicales Internationales, 1988, pp. 127-139; Erythrocyte aggregation, compaction stasis, the Cohnheim Compaction Phenomenon and inflammation. Clinical Hemorheology 9, 1989 (in press).

85. COPLEY, A.L. Capillary permeability, capillary incontinence, compaction stasis and basement membrane breakdown. Bibl. Anat. 7, 148-155, 1965.

86. LEWENHOEK, A. VAN Concerning the circulation and stagnation of the blood in tadpoles. Philosophical Transactions, (For the years 1700 and 1701), London 22, 447-455, 1702.

87. COPLEY, A.L. Agrégation et desagrégation érythrocytaires. In: J.F. Stoltz (Ed.) Hémorhéologie et Agrégation Erythrocytaire. C.R. de Symposium International, Genève, Suisse, Janvier 1986. Paris: éditions Médicales Internationales, 1986, pp. 9-21; On erythrocyte aggregation and desaggregation. In: J.F. Stoltz (Ed.) Erythrocyte Aggregation. Proc. Internat. Symposium, Geneva, Switzerland, 11 January 1986. Clinical Hemorheology 7, 3-14, 1987.

88. COHNHEIM, J. Lectures on General Pathology (Translated by A.B. McKee from Vorlesungen, the German edition published in 1882). London: New Sydenham Society, 1889, vol. 1, chapter 3, pp. 109-171.

89. COPLEY, A.L. and SEAMAN, G.V.F. (Eds.) Surface Phenomena in Hemorheology. Their Theoretical, Experimental and Clinical Aspects. New York, 26-29 October 1982. Ann. New York Acad. Sciences 416, 1983, 769 pp.

90. STOLTZ, J.F. Fåhræus Award Lecture: The importance of rheological theory in clinical hemorheology. Clinical Hemorheology 8, 293-303, 1988.

91. COPLEY, A.L. Bleeding time, other in vivo hemostasis tests and the arrest of hemorrhage. Thrombosis Research 4, 1-23, 1974.

92. COPLEY, A.L. and SILBERBERG, A. BIORHEOLOGY in its twenty-fifth year of publication. Biorheology 25, 1-4, 1988.

93. COPLEY, A.L. On the validity of classical fluid mechanics in biorheology. In: A.L. Copley, Ed. (6), pp. 3-10.

94. SKAGIUS, K. Biographical sketch of Professor Robin Fåhræus. In: A.L. Copley, Ed. (62), pp. 33-34.

95. COPLEY, A.L. Presentation of Poiseuille Award to Professor Robin Fåhræus. In: A.L. Copley, Ed. (62), pp. 35-36.

96. COPLEY, A.L. - ALCOPLEY, L. Portrait of Robin Fahraeus. Notes on a line drawing for the Fahraeus Award. Clinical Hemorheology 3, Nr. 3, i, ix-x, 1983.

97. COPLEY, A.L. Notes on the Fåhræus Medal. Clinical Hemorheology 1, 415-417, 1981.