Robin Fåhraeus: evolution of his concepts in cardiovascular physiology

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Fåhraeus was a pathologist at the University of Uppsala in Sweden, and his interest in the suspension stability of blood and later in the rheology of blood was motivated by the desire to understand the clinical effects of abnormalities in the aggregation and flow behavior of the formed elements. It is ironic to note, in passing, that the main impact of his work and his ideas were, and are, not in clinical medicine, in particular hematology, but rather in physiology. At the time he wrote his doctoral dissertation on the suspension stability of the blood (16), research in the biomedical sciences in Europe was the preserve of researchers interested in clinical problems, and it was they who, in the second half of the 19th and in the first two decades of the 20th century, had provided a substantial body of results on the pressure-flow relation of blood in glass capillaries (18, 30). The aim of most of these studies had been to ascertain whether blood, amphibian or mammalian, obeyed the law of Poiseuille (30). Poiseuille had provided these investigators with an unequalled example of precision and meticulousness in carrying out the experiments on the flow of liquids through narrow tubes (47). It was Hess (30), in 1915, who put 50 years of work in perspective and concluded (correctly as it turned out) that blood obeys Poiseuille’s law only in the limit of high flow and shear rates. The non-Newtonian effects, as evidenced by an increased apparent viscosity at low flow rates were, Hess believed, due to the elastic deformation of the red cells. He thought it plausible that the ability of the red cells to form rouleaux would play a role in what we would now call the viscoelastic behavior of blood. Hess (30) argued against those, such as Thoma (59), who thought that the decrease in viscosity with increasing flow rate was due to the existence of a flow-dependent peripheral cell-free layer. Such a layer had been described as early as the 18th century by Leeuwenhoek and Boerhaave in capillaries (20) and later by Poiseuille in the frog mesenteric microcirculation (47). What these pioneers had also seen under the microscope was the aggregation of red cells in plasma (20,
Strange as it may seem to us today, the aggregation of red cells and the effect on sedimentation velocity did not enter the discussion of the non-Poiseuillian flow behavior of blood in glass tubes. This was so despite the earlier remarkable observations on the effect of flow rate on blood cell spatial and velocity distribution in horizontal and vertical tubes by Schklarewsky in 1868 (52). However, it was generally agreed that the inward migration of blood cells was due to an inwardly directed pressure gradient resulting from velocity differences in the laminae of the sheared suspension, which drives particles of “high density” (red cells) toward the tube axis, leaving particles of “low density” (white cells) at the periphery. Some investigators thought that the changes in blood viscosity with flow rate were only of minor significance in the circulation, since “the organism has a simple means of regulating vessel cross-sectional area through which the effect of even the most marked viscosity changes on the total resistance can be compensated for, so that the magnitude of the viscosity coefficient is quite irrelevant as far as the circulation is concerned” (translated from the German, Ref. 30). Hess (30) did not subscribe to this view, since he felt that the relationship between the behavior of blood and the hemodynamics was complex and had not yet been elucidated.

At this point in time, Fahraeus enters the scene, quite accidentally it appears, in 1917, through his observation that the sedimentation velocity of red corpuscles increases during pregnancy. It was a well-known fact, dating back to antiquity, that after blood letting in sick persons and pregnant women, the buffy coat which formed during coagulation was absent in the case of healthy individuals (16, 18). Some had correctly explained this difference as being due to the greater sedimentation rate of the cells in the “unhealthy blood”; thus revealing the buffy coat before coagulation stopped further sedimentation. However, studies of the problem ceased in the first half of the 19th century after years of intense interest. Fahraeus used the question of the buffy coat as the starting point for his work on red cell sedimentation and the more general problem of the suspension stability of the blood. He pointed out that fibrinogen was the principal protein involved in red cell aggregation leading to the formation of regular rouleaux and that the process was quite distinct from blood coagulation. He applied colloidal chemical principles to qualitatively describe the stability of the suspension (16, 18). More relevant to modern circulatory physiology was the subsequent study of the effect of aggregation on the “streaming blood” (18, 19) and the more general relation between blood cell distribution in vessels and the velocity and apparent viscosity of blood (21). It is remarkable with what clarity he understood and how forcibly he expressed his views on the phenomena occurring in the tube flow of mammalian blood. The following were his conclusions (17). 1) At high flow rates in tubes of diameters &lt;0.3 mm, the concentration of red cells (hematocrit, H_r) is lower than that in the larger feed tube (hematocrit, H_T) because the red cells are distributed in an axial core, and their mean velocity is therefore greater than the mean velocity of the blood. There is a reciprocal relationship between H_T and the mean cell velocity in the tube. H_T/H_r decreases with decreasing tube diameter. 2) As a consequence of the lower red cell concentration in the tube, the measured viscosity in tubes of &lt;0.3 mm diameter (computed using Poiseuille’s law) is lower than in a tube of large diameter and decreases with decreasing tube diameter. 3) The migration of blood cells from the tube wall toward the tube axis depends on particle size and not on particle density. Fahraeus thought that Bernoulli’s theorem shows that there is a pressure gradient from wall to axis: the larger the particle, the greater the force pushing it toward the axis. Hence, it is the large white cells that are more axially distributed in the tube than the red cells and whose mean velocity is greater than that of the red cells. Also, in the advance of a meniscus of blood into an empty tube, it is the white cells that accumulate first at the meniscus, forming a white plug at the blood-air interface. 4) At low flow rates, the red cells aggregate into rouleaux, and these being the largest particles in the suspension, migrate to the axis forming a core that displaces white cells to the periphery. Therefore, the concentration of white cells in the tube will be greater than that in the feed tube, and their mean velocity will be lower than that of the red cells and the plasma. The formation of an even wider marginal cell-free zone at low flow rates is expected to decrease the resistance of flow.

The effect described in the first conclusion is known as the Fahraeus effect and that in the second conclusion as the Fahraeus-Lindqvist effect. It has been customary to associate these with a decrease in cell concentration and apparent viscosity, respectively. However, it is clear from the fourth conclusion that Fahraeus realized that the reverse, an increase in tube particle concentration, can occur. Some investigators have termed this a reverse or negative Fahraeus effect. We prefer to include both in the term “Fahraeus effect,” since, after all, the essence of the phenomenon lies in a redistribution of suspended particles, a fact which Fahraeus understood very well. Moreover, the two effects are also well known in physical and colloid chemistry (28).

Why then if the effects are so clearly demonstrable and have such obvious explanations is there so much literature on both the Fahraeus-Lindqvist effect (beginning with work in the 1940s; Refs. 2, 10, 23) and the Fahraeus effect (work beginning in the 1960s; Ref. 8)? There are three reasons for this. 1) The actual experiments carried out by Fahraeus and his students on the effect of tube diameter on blood cell concentration and viscosity were surprisingly few in number, and nearly all data stem from three papers (17, 21, 62). Moreover, despite the clear assertion that white cells are forced into the tube periphery by the aggregates of red cells, the effect of aggregation was never studied quantitatively in vitro or in vivo. All experiments, whether on cell concentration or viscosity of blood, were carried out at high pressure gradients, ≥8 mmHg/cm, at which none of the low flow rate effects would become apparent. This left several questions unanswered, in particular whether H_T/H_r continues to decrease as the tube diameter approaches and becomes smaller than that of the red cell. Fahraeus thought that in a capillary, in which Krogh (37) had shown that red cells flow in single file, H_T/H_r = 1 (17).
2) The entry into areas of blood rheology and circulatory physiology of investigators trained in the physical and engineering sciences, beginning in the late 1950s, spawned a large number of in vitro studies of blood flow in tubes as well as in Couette and cone-in plate viscometers. 3) The development of sophisticated techniques for the study of pressure, flow, and hematocrit in the vessels of the microcirculation in recent years has made it possible to assess the importance of the Fähraeus and Fähraeus-Lindqvist effects in the living animal and has led to conceptual advances, such as the generalization of the phenomena for microvessel networks as discussed in Definitions of the Effects and in Vivo Applications.

Before describing the more important advances in the study of the two effects, we wish to give a brief mathematical definition of the phenomena and to review the mechanisms of particle lateral migration in tubes.

Definitions of the Effects

Fähraeus Effect

Although the change in average concentration of particles in a suspension that occurs in flow from a large into a small diameter vessels is referred to as the Fähraeus effect, the phenomenon is not to be confused with a diminution of particle concentration in the smaller vessel because of an entrance effect whereby particle entry into the smaller vessel is hindered. To separate this “screening effect” from the true Fähraeus effect, one needs to compare the particle concentration in the suspension in the larger feed vessel (hematocrit H_F in the case of red cells) with that in the suspension flowing from the smaller vessel (hematocrit H_D). In steady flow and in the absence of a screening effect, H_F = H_D (24).

Some of the consequences of the Fähraeus effect can be shown by referring first to the case of steady blood flow through a cylindrical tube. In such a flow, cell and plasma velocities decrease with radial distance from the tube axis, with the highest velocity at the vessel center if the cell distribution is axisymmetric, but not necessarily so if the cell distribution is not axisymmetric. In steady flow, the average number of cells (Ni) with velocity ui crossing a fixed cross-sectional area (A) in the time interval At is given by the equation

$$N_i = (u_i At) \left( \frac{n_i}{L} \right)$$  \(1\)

where \((u_i At)\) is the axial distance traveled by the cells with velocity \(u_i\) in the time interval \(At\), and \((n_i/L)\) is the average number of such cells distributed along the axial distance \(L\). If both sides of this equation are divided by \(A\) and multiplied by \(\bar{V}_r\), the red cell volume, and if \((LA)\) is recognized as the vessel volume containing the \(n_i\) cells, then we can write

$$\frac{N_i \bar{V}_r}{A At} = u_i = u_i (H_T);$$  \(2\)

where \(q_i\) is the volumetric flux of such cells across a vessel cross-sectional area, and \((H_T)\) is the vessel hematocrit of cells with velocity \(u_i\). Equation 2 illustrates a key relationship between parameters. For a given \(q_i\), changing \(u_i\) forces \((H_T)\) to change in the opposite direction, e.g., if the velocity increases for a population of cells (when flux is constant), then their concentration in the vessel must decrease, or alternatively, if several classes of cells are flowing through a vessel, each with the same flux, the fastest cells will be present in the vessel with the lowest concentration (cell concentration is inversely proportional to cell velocity).

The total flux of cells through a vessel cross section can be obtained from Eq. 1 by summing the contributions of cells of all velocities

$$\sum N_i = \Delta t \sum u_i \left( \frac{n_i}{L} \right)$$  \(3\)

The discharge hematocrit is then obtained by converting the total cell number flux to total volume flux by multiplying by \(\bar{V}_r\) and dividing by the total blood flow rate \((\bar{A}\bar{u})\), where \(\bar{u}\) is the average blood velocity

$$H_D = \frac{\bar{V}_r \sum N_i}{\bar{A} \Delta t} = \frac{\bar{V}_r}{\bar{A} L} \sum u_i n_i$$  \(4\)

The vessel hematocrit \((H_T)\) can be determined as

$$H_T = \frac{\sum n_i \bar{V}_r}{AL} = \frac{\bar{V}_r}{AL} \sum n_i$$  \(5\)

Dividing Eq. 5 by Eq. 4 gives

$$\frac{H_T}{H_D} = \frac{\bar{u}}{\sum n_i/u_i n_i} = \frac{\bar{u}}{\bar{u}_c}$$  \(6\)

since \(\sum u_i n_i/\sum n_i = \bar{u}_c\), which is by definition a number average cell velocity (7). Alternatively, \(\bar{u}_c\) is equal to the harmonic mean of the velocities of all cells crossing a fixed cross section of the vessel. In terms of the average cell and plasma velocities, the equivalent equation to Eq. 6 is

$$\frac{H_T}{H_D} = \frac{\bar{u}_p}{\bar{u}_c} (1 - H_T) + H_T$$  \(7\)

where \(\bar{u}_p\) is the average plasma velocity. These latter two equations demonstrate that \(H_T/H_D\), which is a numerical measure of the Fähraeus effect, will change proportionately with changes in \(\bar{u}/\bar{u}_c\) (from Eq. 6), whereas the effect of changes in \(\bar{u}_p/\bar{u}_c\) on \(H_T/H_D\) is more complex, depending also on the value of \(H_T\).

Fähraeus (18) set \(\bar{u}/\bar{u}_c\) equal to \(H_T/H_D\), showing that he had used the equality in Eq. 6 without stating how he knew that this equality existed.

So far, consideration has been given only to flow in one vessel. The flow in a vessel can be imagined to consist of parallel flows in which fluid elements with the same velocity flow in separate (imaginary) tubes within the vessel. Such imaginary separation of the flow of fluid elements does not affect the mathematical description thus far presented. It is evident, therefore, that the analysis can be applied to the case of simultaneous flows in parallel vessels, and furthermore, that the extension does not require that the vessels be parallel or separate as long as we consider all the fluid flows that enter or
leave a volume of tissue completely enveloped by a continuous surface. These extensions are referred to below.

The limits of the values for $H_T/H_D$ depend on the physics of the situation being considered. In the case of flow in a single vessel, there are two physical empiricisms that must be observed: 1) the fluid velocity goes to zero at the vessel wall, and 2) the apparent viscosity of the suspension at a given shear rate increases with increasing cell concentration. As a consequence, in a circular cylindrical vessel the minimum value of $\bar{u}/\bar{u}_c$ is 0.5 for the case of flow at very low hematocrit in which the cells flow in single file down the centerline of a large circular cylindrical vessel; any movement of cells from the centerline results in higher $\bar{u}/\bar{u}_c$ values because the velocity profile in such a flow is parabolic with the maximum velocity at the centerline. In the case of normal hematocrits, the velocity profile is blunted from the parabolic because of particle crowding in the suspension (27, 28), an effect which is further enhanced by the nonNewtonian flow properties of the blood and by an increased red cell concentration in the core of the tube. The latter effect is particularly strong at very low flow rates in vertically positioned vessels when red cell aggregation leads to the formation of a centrally located network of rouleaux surrounded by a cell-depleted peripheral plasma layer. Here, $\bar{u}/\bar{u}_c$ lies between 0.5 and 1.0. If the blood flow is such that the cells are peripherally distributed, in the low-velocity region, a high value of $\bar{u}/\bar{u}_c$ results and is possibly much greater than unity. This situation can arise either because of hydrodynamic forces causing a net migration of cells away from the tube axis [as in the tubular pinch effect (25, 55) where particles reach an equilibrium radial position located between tube axis and wall] or at very low flow rates in horizontal tubes because of aggregation and sedimentation of cells onto the lower vessel wall. In the capillaries, if the cell effectively fills the vessel lumen, $\bar{u}/\bar{u}_c$ is very close to unity. Thus, for single circular cylindrical vessel flows, $\bar{u}/\bar{u}_c$ (and therefore $H_T/H_D$) is limited to values of 0.5 and larger.

For vessels that do not have a circular cylindrical lumen, this limit on $H_T/H_D$ need not apply. For example, if a vessel wall is severely convoluted, it is possible that the fluid regions within vessel wall folds contain only plasma, which may travel with an average velocity that is markedly different from the average velocity of the blood in the central region of the vessel. If all the fluid volume space is included in the calculation of $H_T$, then it is possible for $H_T/H_D$ to be less than or greater than 0.5.

In considering blood flow in networks of vessels, there are no necessary relationships between velocity and hematocrit in a given vessel; a vessel containing high hematocrit blood can have a high or low flow rate, and the same is true for a vessel with low hematocrit blood. Consequently, the ratio of the average hematocrit of all the blood contained in the network (tissue hematocrit, $H_T$) to the hematocrit of the blood flowing into the network ($H_D$) can have any positive value, including those $<0.5$.

**Fähraeus-Lindqvist Effect**

The original observation that the flow resistance of blood and other red cell suspensions decreases as vessel diameter decreases below about 300 μm (21) has come to be called the Fähraeus-Lindqvist effect.

It has become customary to use the Poiseuille-Hagen equation to describe the relationship between the variables that govern blood flow through a cylindrical vessel

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

where $Q$ is the suspension volumetric flow rate through a tube of radius $R$ under a pressure difference $\Delta P$ over the vessel length $L$; $\eta$ is an effective viscosity, which must be empirically determined because the restrictions used in deriving this equation (laminar flow of a Newtonian continuum fluid) are usually not met in blood flow through small vessels. (The term "apparent viscosity" is generally defined as the ratio of shear stress to shear rate, and for a nonNewtonian or a noncontinuum fluid flowing in a cylindrical vessel, this ratio varies across the vessel lumen, making $\eta$ some average of the values of the ratio. For a Newtonian continuum fluid, $\eta$ and the fluid apparent viscosity would be equal.) Rearrangement of Eq. 8a gives a means for evaluating $\eta$ from measurable quantities

$$\eta = \frac{\pi R^4 \Delta P}{8LQ}$$

Often, the effective viscosity is divided by the viscosity of the suspending medium to give the relative viscosity. Because the suspending medium (plasma or serum) viscosity is not a function of vessel size or flow rate, the relative viscosity is proportional to the effective viscosity.

The finding that the relative viscosity of a red cell suspension decreases as vessel diameter decreases could be due to a number of factors. It may be simply due to the Fähraeus effect, i.e., a lower viscosity of the suspension caused by the lower hematocrit in the vessel; it may also be due to the rheological effect of a nonuniform distribution of cells across the vessel lumen or to the failure of the continuum model of the suspension (see FLUID MECHANICAL CONSIDERATIONS). The fact that all three of these factors can be reasonably expected to contribute to the Fähraeus-Lindqvist effect in blood has prevented resolution of the question of the relative contribution of these factors to the effect.

Most of the earlier data on the Fähraeus-Lindqvist effect were obtained under flow conditions effectively preventing red cell aggregation. However, as pointed out above, at low shear rates red cell aggregation leads to different effects. On aggregation, red cells have the tendency to exhibit syneresis so that the mass of red cells contracts on itself; during flow in a tube, this alone results in the pulling of the red cells into the center of the vessel, leaving a larger layer of low-viscosity suspending medium near the vessel wall (resulting in a lowering of flow resistance). However, aggregated red cells also have an increased tendency to sediment. Fähraeus, of course, was very much interested in the relationship between red cell aggregation and sedimentation.

Red cell sedimentation in living vessels and its pathological significance were extensively studied by Knisely (36) who used the term "sludged blood" for intravascular erythrocyte aggregation, which in his view, in clear con-
tradition to Fåhraeus' concepts, was an exclusively pathological phenomenon. The effect of increased red cell sedimentation on flow resistance depends on the orientation of the vessel in the gravitational field. In a vertically oriented vessel, the gravitational effect accelerates or decelerates the central core of red cell-rich fluid depending on flow direction. This has a minor effect on the flow resistance. Regardless of the flow direction, red cell syneresis causes an increased axisymmetric suspending medium layer at the vessel wall that results in a decreased flow resistance (26, 50). In a horizontal tube, sedimentation causes a nonsymmetrical distribution of red cells onto the bottom of the tube, which is found to result in increased flow resistance (50). (On the basis of earlier discussion, it is clear that syneresis-sedimentation effects will also affect the magnitude of the Fåhraeus effect, although this has not been experimentally investigated yet). The sedimentation causes transient changes in overall vessel hematocrit, but because of the slowness of the flow, this effect is seen as a very slow change in overall flow conditions, although it does depend on the ratio of the total vessel length to the average fluid velocity.

**FLUID MECHANICAL CONSIDERATIONS**

The redistribution of blood cells in narrow tubes, which is at the root of the Fåhraeus and Fåhraeus-Lindqvist effects, is due to a net lateral migration of the particles away from the vessel wall. Fortunately, there exists today a substantial body of theoretical and experimental knowledge on the effect of the vessel wall on the motions of suspended particles in model dispersions and blood. The reader is referred to reviews of the subject by Brenner (5) and Leal (38). From these studies, carried out over the last 30 years, it is clear that both the particle density-dependent hypothesis of Schklarewsky (52) and the particle size-dependent hypothesis of Fåhraeus (17) for inward migration of blood cells in flow through circular tubes are false. Both invoke the Bernoulli theorem to prove that there is a radial pressure gradient across the tube that results in a force moving particles from tube wall to axis. The more common expressions of Bernoulli's theorem do not account for viscous dissipation of energy and therefore apply strictly only to an inviscid fluid and can at best only be used for real, viscous fluids at high tube Reynolds number when inertial forces dominate viscous forces. The more complete version of Bernoulli's theorem, as well as the application of the laws of conservation of momentum, show that there is no radial pressure gradient in the tube. Rather, it is the wall together with the inertia of the fluid that produces migration effects, as described below.

**Dilute Suspensions**

In dilute suspensions of model particles and blood cells undergoing laminar viscous (Poiseuille) flow through a circular tube, particle radial migration can occur through two mechanisms (5, 25, 29, 38). 1) Migration occurs through lateral movement toward the tube axis of deformable particles (liquid drops, flexible fibers, red blood cells, and rouleaux) at low Reynolds number under creeping flow conditions (negligible inertial effects). Such migration persists at higher Reynolds number when inertial effects become significant. In the case of liquid drops it has been shown to be due to an inwardly directed force arising from the interaction of the flow field around the deformed drop with the tube wall (5, 6). 2) Migration also occurs through two-way lateral movement to an eccentric radial equilibrium position of rigid particles (spheres, cylinders, and aldehyde-fixed red blood cells) initially located either near the wall or near the axis, at higher Reynolds numbers at which inertia of the fluid is significant. In this, the "tubular pinch effect" (55), migration becomes appreciable at particle Reynolds number ($Re_p > 10^{3}$), where

$$Re_p = \frac{4}{3} \frac{b^2}{R^2} \frac{\rho}{\eta}$$

Here, $b$ and $R$ are the respective particle and tube radii, $U$ is the mean linear fluid velocity in the tube, and $\rho$ and $\eta$ are the respective fluid density and viscosity.

The migration velocities in both mechanisms vary as the third power of the ratio of particle to tube radius, and the inward migration velocity falls off rapidly with increasing distance from the tube wall. For migration at higher Reynolds number, theory shows that the effect has its origin in inertia of the fluid and in the interaction of the particle with the wall (5, 12, 38). The effect may be likened to the curving of a spinning tennis ball (Magnus effect), although it should be noted that nonrotating particles also migrate, and the presence of the wall is an essential feature of two-way migration. In Fåhraeus' experiments, conducted at 100-mmHg pressure in a 10-cm long tube of 0.3 mm diameter, the estimated mean velocity ($U$) equals 89 mm/s, assuming Poiseuille's law and a high shear rate blood viscosity of 3.5 mPa·s. This yields a $Re_p$ value of $3.8 \times 10^{3}$ for red cells (equivalent sphere radius of 2.8 $\mu$m) and $1.1 \times 10^{4}$ for the larger white cells ($b = 4 \mu$m). The tubular pinch effect has been observed with normal as well as glutaraldehyde-fixed red cells at $Re_p > 10^{4}$ (25), and the migration velocity has been shown to increase with increasing $b/R$ and $U$. White cells in plasma also migrate appreciably inward from the tube wall at $Re_p > 10^5$ (29). Thus Fåhraeus was correct in believing that the migration effect was particle size dependent.

The above considerations apply to suspensions of neutrally buoyant particles. It is of interest to note that for nonneutrally buoyant particles, the equilibrium position for flow in vertical tubes in the tubular pinch effect is shifted to the wall for a particle sedimenting in the direction of the flow and is shifted toward the axis for a particle sedimenting in a direction opposite to that of the flow (5). The condition for such effects to become important is that ($b/R)^2 \ll u_w/U \ll 1$, with $u_w$ being the sedimentation velocity. In the case of Fåhraeus' experiment, $u_w \approx 10^{5}$ and $5 \times 10^{2}$ mm/s for red and white cells, respectively, thus $u_w/U \ll (b/R)^2$ in the 0.3- and even in the 0.1 mm diam tube, with mean fluid velocities of 50–90 mm/s. The system was thus effectively neutrally buoyant, and Fåhraeus was correct in stating that Schklarewsky's density-dependent migration theory was wrong.
Concentrated Suspensions

It may seem ironic that the law enunciated by Poiseuille from his work on simple Newtonian fluids (Eq. 8a) should fail to apply to suspensions of blood cells, since the object of his research was to arrive at an understanding of flow in living vessels. However, such non-Newtonian behavior is quite characteristic of many suspensions of large and small particles. Ever since the time of Bingham it has been known that the effective viscosity of clays, paints, and other suspensions measured in capillary instruments decreases with increasing flow rate and decreasing tube diameter (3). To account for these anomalous effects, three main theories have been proposed.

Hydrodynamic wall effect. Van (61) showed that in the presence of a rigid boundary a flowing suspension of rigid spheres of radius \( b \) behaves as if there were a layer of thickness, \( h \), equal to 1.302\( b \) at the wall, having a viscosity equal to that of the suspending medium. The true (\( \eta_r \)) and effective (\( \eta'_r \)) relative viscosities are related by

\[
\frac{1}{\eta_r} - 1 = \left( \frac{1}{\eta'_r} - 1 \right) \left( 1 - \frac{h}{R} \right)^{-4}
\] (9)

The theory therefore predicts that \( \eta'_r \) decreases with decreasing tube radius.

Summation or “Sigma hypothesis.” This is based on the presumed existence of unsheared laminae within the suspension that produce a stepwise velocity distribution, the integral in the derivation of Poiseuille’s equation being replaced by a summation. This approach is an empirical one and has been applied to clay pastes and flowing blood (53), but it has not been possible to relate it to the problem of dilute suspensions of spheres.

Axial migration of particles. Inward particle migration across the planes of shear, which as described above certainly occurs in dilute suspensions, also plays a part in concentrated suspensions, emulsions, and blood. From in vivo and in vitro studies at high flow rates (no red cell aggregation), it appears unlikely that, at hematocrits of 0.40–0.45, the plasma-rich peripheral zone can be much larger than 4 \( \mu m \) in vessels the diameters of which \( >100 \mu m \). Nevertheless, an inward migration by only one-half particle diameter from the wall brings about a significant decrease in the average particle concentration in the tube (Fähraeus effect, Refs. 1, 56). This results in a significant decrease in the energy dissipated in the flow and a decreased effective viscosity, as shown by experiment and calculation in blood (44, 60) and model particle suspensions (33, 57).

Experimental Data

The published experimental data describing the Fähraeus and Fähraeus-Lindqvist effects are shown in Figs. 1 and 2, respectively.

Fähraeus Effect

Figure 1A indicates the range of values found for the Fähraeus effect for the situation in which the hematocrit in the feed vessel is 0.40–0.45 and the conditions do not permit red cell aggregation. The only points drawn are for Fähraeus’ original data (18). It is evident that, at a given vessel diameter, the data cover a relatively large range of concentrations. This is in part due to imprecise experimentation and methodology (e.g. in most cases \( H_n \) was not directly measured but assumed equal to the feed hematocrit), but it may also be due to a real dependence of the Fähraeus effect on parameters in addition to vessel diameter and feed hematocrit, such as shear rate. There is also the possibility that some of the scatter is due to differences between experimental conditions, since investigators used different suspending media (saline and plasma) and different temperatures (room temperature and 37–38°C).

The Fähraeus effect does depend on the level of the feed hematocrit. \( H_T/H_D \) at a given vessel diameter decreases with decreasing \( H_T \), the decrease being larger for smaller vessels.

As mentioned earlier, red cell aggregation under low flow or pathological conditions will affect the Fähraeus effect; it is expected that movement of cells into higher velocity (central) regions will cause a decrease in \( H_T/H_D \), whereas movement of cells toward lower velocity (wall) regions will cause an increase in \( H_T/H_D \). This has not been adequately researched.

Figure 1B shows the data from human white cells (29, 45, 46, 62) and platelets (11, 58) flowing in blood through cylindrical tubes. In keeping with the widespread observations that at high flow rates white cells are preferentially located in the central region of a vessel but that they migrate to the vessel perimeter as the flow rate decreases allowing red cell aggregation to occur, the data in Fig. 1 show that at higher shear rates (flows) the ratio of cell number concentration in the tube to that in the discharge (\( C_T/C_D \)) is lower than at lower shear rates. The data from Goldsmith and Spain (29) and Nobis et al. (46) clearly demonstrate this. With respect to the data of Nobis et al. (46), it should be pointed out that these points were calculated from published experimental concentration profiles, assuming a parabolic velocity profile. Because the velocity profile is undoubtedly blunted from the parabolic (27), the calculated \( C_T/C_n \) values underestimate the real values.

The platelet data always show \( C_T/C_D \) to be greater than unity as long as red cells are present; in the absence of other cells, \( C_T/C_D \) is less than unity for platelets. This is consistent with the finding that platelet concentration in blood is greatest near the vessel wall. The datum point from Tangerdler et al. (58) is calculated from concentration profile data, by the method used for the Nobis et al. (46) white cell data, and is similarly an underestimate of \( C_T/C_n \).

All these data are consistent with the general concept, applicable to the tube flow of any suspension or emulsion, that the concentration of particles within the tube depends on their radial distribution. The concentration in the tube is greater than that in the discharge from the vessel if the particles are preferentially located in lower velocity (wall) regions and vice versa.

Fähraeus-Lindqvist Effect

Figure 2 illustrates the Fähraeus-Lindqvist effect for blood flow through tubes under various conditions. The
FIG. 1. Fåhraeus effect as demonstrated by literature data. A: Fåhraeus effect for human red cells, feed hematoctrit 0.40–0.45; all data collected for red cell suspensions flowing through cylindrical tubes at flow rates ensuring no red cell aggregation. Cross-hatched region contains all literature data; only points of Fåhraeus’ data (18) are shown. Critical diameter (~2.7 μm) is that of smallest cylindrical vessel through which a human red cell can flow. H_f/H_o, numerical measure of Fåhraeus effect. B: Fåhraeus effect for human white cells and platelets. C_p/C D is ratio of number concentration of cells in blood in tube to that in discharge from tube.

White Cells
- Vejlens (1938) Lymphocytes
- Vejlens (1938) Granulocytes
- Nobis and Gaehtgens (1981)
- Nobis et al. (1982)
- Goldsmith and Spain (1984)

Platelets
- Corattiyl and Eckstein (1987)
- Tangelder (1982)

White cell data show expected effect of shear rate (flow rate). Data of Vejlens (62) and of Nobis and Gaehtgens (45) were obtained at high shear rates. Data of Goldsmith and Spain (29) were obtained at mean shear rates from 48 to 88 s⁻¹ for 150-μm tube and from 36 to 118 s⁻¹ for 100-μm tube, and those of Nobis et al. (46) were obtained at mean shear rates from ~43 to 330 s⁻¹. Dashed lines with arrows pointing in direction of increasing shear show how Fåhraeus effect changes with increasing shear rate. Points from Nobis et al. (46) were calculated from published concentration profiles with assumption of a parabolic velocity profile. Platelet data of Corattiyl and Eckstein (11) show a maximum C_p/C D for an apparent wall shear rate of 800 s⁻¹. In shear rate range of 80–8,000 s⁻¹, C_p/C D decreased from these maximum values to minimum values indicated by lower circles. Tangelder point (58), obtained at a mean shear rate ~890 s⁻¹, was calculated from in vivo concentration profiles, assuming a parabolic velocity profile. All these C_p/C Ds must approach unity as vessel diameter decreases.

The cross-hatched area contains all the literature data for flow rates at which red cell aggregation is prevented (including all those in Ref. 23 and in all subsequent data); the only points shown are those from the data of Fåhraeus and Lindqvist (21). As before, differences in relative viscosity at a given tube diameter reflect the fact that experiments were conducted with red cells suspended in various media and at different temperatures.

Attempts to predict the observed dependence of relative viscosity on tube diameter on the basis of the Fåhraeus effect, assuming that hematocrit is uniform across the vessel lumen and that fluid viscometric data obtained in Couette and cone-in-plate instruments are applicable, have met with varying degrees of success in the hands of various investigators, both with in vitro and in vivo data. Two-phase flow models with a plasma wall layer and a core region of uniform or nonuniform hematocrit have also been applied to the data and yield values for free parameters in the models (such as wall layer thickness). The calculated parameters often seem physically plausible but do not validate such models.

At very low flow rates in horizontal tubes, where red cell aggregation and sedimentation occur, the flow resistance, as reflected in the relative viscosity, increases with decreasing apparent wall shear rate (flow rate). For such a two-phase flow just one curve is shown, which is that for wall shear rates of 1.0-4.0 s⁻¹ (50).

At very low flow rates in vertical tubes, the red cells aggregate and migrate into the vessel core, forming a plasma layer at the wall. The thickness of the peripheral plasma layer increases with decreasing flow rate until a constant value is reached. The relative viscosity mirrors the growth of the plasma layer, decreasing until the wall layer thickness is constant (26). The lower curves, marked P and D, show the minimum relative viscosities found for red cells in plasma and plasma plus Dextran 250, respectively (50). In the presence of Dextran 250, the red cells aggregate more strongly than in plasma alone, resulting in a more densely packed central region of red cells and a thicker wall layer of suspending medium.

For very small vessels, the diameters of which approach that of the red cell, no aggregation or sedimentation is possible, so all curves must converge. In these smallest vessels, relative viscosity increases dramatically as vessel diameter approaches 2.7 μm, the approximate
size of the smallest vessel through which a human red cell can travel without rupture. The large rise in the rate of increase in relative viscosity is primarily due to the small clearance between the individual red cell and the vessel wall.

IN VIVO APPLICATIONS

Fähræus’ theoretical and experimental work was conceived as an effort toward a better understanding of the blood flow behavior in the circulatory system and particularly its "business end," the microcirculation. Nevertheless, Fähræus does not appear to have tested his concepts by in vivo experiments directly. Although other investigators (63) provided evidence from whole organ perfusion experiments for the diameter dependence of apparent blood viscosity as early as 2 years after the publication of the Fähræus-Lindqvist paper, it took about 40 years until the development of appropriate methods permitted an evaluation of Fähræus’ concepts in the living microcirculation. Intravital microscopy, however, had for some time been used to obtain at least descriptive information on the effect of red cell aggregation on microvascular blood flow. Such studies led Knisely (36) to the concept of sludged blood as a major cause of increased flow resistance and eventually even circulatory failure under pathophysiological conditions. Knisely’s (36) conclusion that flow stagnation is a consequence of aggregation (or agglutination as he also called it) was, of course, the direct opposite of Fähræus’ conclusions, and a bitter controversy developed between the two men. In the light of today’s knowledge both Knisely and Fähræus were right to some degree. As already pointed out above, red cell aggregation per se, by causing axisymmetric syneresis, reduces rather than increases effective viscosity as was claimed by Fähræus. However, aggregation in the presence of gravitation also leads to sedimentation and nonaxisymmetric syneresis which indeed elevates viscous resistance as postulated by Knisely. It is in a way tragic that the development of our knowledge led to this rather balanced compromise that leaves room for both alternative concepts some 20 years after the death of both contenders.

It was Fähræus himself who stated that the phenomenon, now termed the Fähræus effect, is relevant only in what he called the “paracapillary vessels” (ID <300 μm; Ref. 17). Because the hematocrit in these vessels is a determinant both of resistance to flow and of oxygen transport capacity, quantitative measurements of red cell flux and red cell concentration distributions were undertaken in various tissues. Such measurements inevitably demanded an evaluation of Fähræus’ concepts. In general terms, the data available today clearly demonstrate a substantial reduction of hematocrit in the microcirculation (Fig. 3). This is consistent with the fact that total red cell mass and plasma volume are not distributed evenly but that the average hematocrit of all the blood in a tissue (tissue hematocrit) is usually less than large vessel hematocrit. However, considerable uncertainty developed concerning the mechanisms contributing to the observed hematocrit distribution in microvascular networks. Several aspects emerged that cannot easily be accounted for by the classic Fähræus effect in single microvessels alone, and extensions of Fähræus’ concepts have therefore been undertaken.

1) Although, on the average, hematocrits appear to decrease with decreasing vessel diameter, the extent of hematocrit reduction is greater than predicted from in vitro measurements. In particular, capillary hematocrit in several tissues was found to average ~26–12% of systemic hematocrit (31, 32, 34, 35, 41–43, 49, 51, 54; Fig. 3), whereas the classical Fähræus effect alone does not allow <50%. The question therefore arose about the origin of this “additional hemodilution.” 2) The variability of hematocrit values in vessels of similar dimensions within a given microvessel tree appears to increase toward the true capillaries, in which most studies have reported coefficients of variation of ~50% (Fig. 3). Because this
is clearly more than can be accounted for by error of measurement, additional explanations are required. 3) Capillary hematocrits have been reported to vary with blood flow. Pharmacological and metabolic vasodilation elevates mean capillary hematocrit levels, whereas vasoconstriction lowers capillary hematocrit (34, 35).

Two general avenues of thinking have been utilized to reconcile these findings that cannot be explained by the classical single-vessel Fahraeus effect alone. Both of these accept Fahraeus’ original considerations as well as their applicability to flow in the microcirculation. Although concept A (13, 15, 34) is based on the assumption (supported by direct measurement) that the discharge hematocrit ($H_D$) is the same in all microvessels and therefore $H_T/H_D < 0.5$ requires additional explanation, concept B (9, 48) calls for variation of discharge hematocrit within a microvessel network and maintains that $H_T/H_D \geq 0.5$ for each vessel. Common to both concepts, however, is the conclusion of a relative retardation of the plasma passing through the vessel network, such that the ratio of mean transit times ($t_{RBC}/t_{blood}$) is significantly smaller than unity.

**Concept A**

The value of $H_T/H_D$, as calculated from experimental data, can be $<0.5$ if immobilized plasma volume is included in the calculation of $H_T$ as described in DEFINITIONS OF THE EFFECTS. On the one hand, this has been thought to occur because of noncircular vessel cross sections, e.g., in contracted arterioles which provide “pockets” of plasma not participating in flow. On the other hand, it has been proposed that a layer of plasma is immobilized by the roughness of the endothelial surface (“hairy wall”) caused by an extensive glycolcalyx and microvilli. Quantitatively, the thickness of the layer of plasma required to reconcile the low capillary $H_T$ is in the order of up to $1.2 \mu m$ (13, 15, 34).

The experimental evidence in support of this concept includes measurements of $H_D$ in various arteriolar and venular microvessels by direct aspiration of blood through micropipettes. The data showed values that were not significantly different from systemic hematocrit, $H_{sys}$ (13, 15). In addition, microinjection of heparinase through micropipettes, presumably causing removal of glycosaminoglycans from the endothelial surface, resulted in an elevation of capillary hematocrit (14). These observations support the notion that red cell exclusion from an immobilized plasma layer causes $H_T/H_D$ to decrease below the limit of 0.5. While red cell flow fraction ($H_D$) is constant throughout the microcirculation, red cell volume fraction will decrease in these microvessels in which the surface roughness is significant relative to vessel radius.

Difficulties with this concept arise from the postulate of the surface layer of plasma remaining stationary in the face of a pressure differential that would cause flow of an essentially Newtonian fluid, to say nothing of the very high velocity gradient generated between the stationary surface layer and a passing red cell.

**Concept B**

The low capillary hematocrit could also result from repeated phase separation taking place at the successive microvascular bifurcations preceding the capillary network proper. This would cause variation of $H_D$ between two daughter branches originating from a parent vessel and would therefore lead to corresponding variations of $H_T$. Because of the nonuniform radial distribution of red cells in a parent vessel, red cells and plasma are not evenly distributed at bifurcations, and in general, the faster flowing branch receives the higher hematocrit. However, the elevation of $H_D$ in the faster branch is less than the reduction of $H_D$ in the slower, and the average of the two, just as the mean of the two ensuing $H_{sys}$, is lower than that of the parent vessel (9, 48). Therefore, nonuniform distribution of flow tends to induce a difference in the overall velocity of the red cells traversing the microvessel network compared with that of the plasma.
The mean $H_D$ of the network will be less than the hematocrit of the feeding and draining vessels, and mean $H_L$ will be $<0.5 \, H_{sys}$. This effect is a direct conceptual generalization of the original Fahraeus effect and has therefore been termed the network Fahraeus effect (39, 49). Conceptually it replaces the higher flow velocities in the centerstream of a single vessel by the higher flow velocities in one of the daughter vessels of an arterial bifurcation and assumes that red cells will preferably follow these faster pathways because of phase separation just as they follow the central streamlines in the single vessel because of axial migration.

Evidence in support of this concept has been provided by showing that the observed hematocrit distributions can be explained on the basis of the combined network and single-vessel Fahraeus effects if the topological structure of the microvascular system is known. Furthermore, the high coefficient of variation observed in those studies in which all rather than selected capillaries of a given network were analyzed strongly supports this concept (9, 39).

The physiological implications for oxygen transport to the tissue are quite different in both concepts. Because the product of discharge hematocrit and volume flow is proportional to the oxygen delivery through a microvessel and because the tube hematocrit in the capillaries may influence the local rate of oxygen extraction (22), the presence or absence of supply heterogeneity as well as its possible control by flow-regulating mechanisms critically depends on the clarification of the above issues. This is a problem of considerable general interest, since the exchange efficiency of heterogeneous networks is less than that of homogeneous networks. Several studies have shown beyond doubt that microvesSEL hematocrits increase substantially with vasodilation and vice versa. If this involves changes in discharge rather than only tube hematocrits, oxygen delivery to tissue will not be proportional to blood flow, since the variation of hematocrit will provide a large gain factor.

So far, the differences between experimental observations, as well as the resulting conceptual discrepancies pointed out, represent an unresolved yet physiologically relevant problem. It should be noted that comparisons between hematocrit distributions obtained experimentally in different tissues are complicated by the fact that the detailed structure of the vessel network is often not known and thus may lead to a bias in the procedure for collecting data. Because network structure is clearly important for the resulting dispersion of hematocrits (39), a final resolution of the present discrepancy will have to await more complete information from different tissues and different animal species.

In principle, such considerations, which are derived from Fahraeus’ original concepts, can also be applied to the differential distribution of other blood cells in the vascular system. In the case of white blood cells for instance, uneven intranetwork distribution results from the intravessel radial distribution (4, 40), and this can be affected by red cell aggregation at low flow rates. Therefore, a redistribution of white blood cell delivery to subnetworks of the microvascular system could be brought about by alteration of blood flow. This is of considerable interest in the context of inflammatory reactions and postischemic reperfusion injury.

It turns out that Fahraeus’ original concepts, which were mainly aimed at a better understanding of circulatory hemodynamics, have evolved into complex extensions of fundamental relevance for oxygen transport and its regulation on a local basis. Much less progress has been made in the hemodynamic implications of his work; in particular, the role of red cell aggregation for the resistance to blood flow and its distribution in microvascular networks has still not been identified in vivo despite some efforts. Although the pathophysiology of the cardiovascular system may therefore not have gained so much from pursuit of Fahraeus’ ideas, circulatory physiology obviously has.

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