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THE FLOW OF HUMAN BLOOD THROUGH CAPILLARY TUBES

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SUMMARY

1. The current interpretation of *in vivo* blood flow is mainly based on the Hagen–Poiseuille equation, although blood is not a Newtonian fluid. In this paper, experimental pressure–flow curves of blood are explained on the basis that the viscosity of the blood is the sum of two components, a Newtonian viscosity term, N, and an anomalous viscosity term equal to $A/(B+D)$, where A and B are constants, and D the shear rate.

2. To a first approximation, blood flow in capillary tubes, comparable to that *in vivo*, can be deduced if the applied pressure in Poiseuille's equation is reduced by an effective back-pressure, p, equal to $8Al/3R$, where l is the length of the capillary tube, and R its radius.

3. The theory explains the progressive change, from a parabolic velocity profile in large vessels, to a flattened profile in small vessels, as observed *in vivo*.

4. Experimental evidence is given that p is proportional to the length, and increases with decrease of R. The effect of the anomalous viscosity coefficient A was studied by varying the haematocrit, fibrinogen level, erythrocyte flexibility and temperature.

5. As the tube bore is decreased, the Fahraeus–Lindqvist effect decreases N, but this is offset by an increase of the anomalous component, A. This results, at lower pressures, in an increase of the effective blood viscosity in small vessels and of the peripheral resistance, and, at higher pressures, in a decrease of the effective blood viscosity.

5. Blood flow is proportional to the radius to the power n, where n is a variable that increases with increase of A and decrease of the applied pressure.

INTRODUCTION

It is well recognized that blood flow is non-Newtonian, that is, the viscosity of blood varies with the shear rate and velocity of flow. None the less it is common to find an analysis of *in vivo* blood flow being based on the Hagen (1839) and Poiseuille (1846) relationship, with allowance for the variation of blood viscosity being made by an insertion of its value into this equation. This approach leads to misconceptions about blood flow, and is fundamentally flawed. If blood viscosity varies with shear rate, this term must be included in the development of the pressure–flow relationship,

before integration with respect to shear rate is undertaken. The first objective of the present approach was to ascertain what relationship between blood viscosity and shear rate is consistent with the characteristic change of blood flow rate with pressure shown in Fig. 1*A*. Haynes & Burton (1959) experimentally demonstrated how this basic form was altered by changes of the haematocrit and tube bore. A review of earlier attempts to resolve this problem has been given by Bayliss (1962).

Another aspect of blood flow is the concept of peripheral resistance, as determined by flow through the microcirculation. This again is commonly based on the Newtonian relationship that flow is proportional to the radius taken to the fourth power, after making allowance for the interaction of the radial geometry with blood viscosity. Whittaker & Winton (1933) attempted to resolve whether, in small blood vessels, the viscosity of blood decreased (Fahraeus & Lindqvist, 1931), was unaltered (Hess, 1912), or increased (Denning & Watson, 1906). It may be, however, that all three possibilities can occur in appropriate circumstances. The results of Whittaker & Winton appeared to confirm the Fahraeus–Lindqvist effect. Other data by Prothero & Burton (1962) support this conclusion. However, in all three cases where a decreased resistance was observed, the blood had been manipulated, prior to the experiments, in such a way as to make it predominantly Newtonian in character. So, as Bayliss observed, it could be 'that the (Fahraeus–Lindqvist) effect does not depend on the existence of non-Newtonian properties of the blood itself'. When other published data, such as those of Haynes and Burton, are analysed more thoroughly, as is discussed later, a decrease of tube bore increases the apparent viscosity of blood. A similar increase of peripheral resistance occurs in pathological situations, which has never been adequately explained.

A theoretical interpretation of blood flow through capillary tubes is given in the Appendix, which establishes the relationship that must pertain between blood viscosity and shear rate, to account for the blood flow–pressure characteristic shown in Fig. 1*A*. Some readers may find it more logical to read this section first. The flow of blood through capillary tubes can be explained on the basis that the viscosity of blood is the sum of two components, a Newtonian viscosity term, N, and an anomalous viscosity term equal to $A/(B+D)$, where A and B are constants, and D the shear rate. An experimental investigation has been undertaken to test the main theoretical implications, in respect of factors that modify the anomalous component, A, and variation of the length and bore of the capillary tube. The experiments were also undertaken to confirm the theoretical deduction that the anomalous viscosity of blood has more influence on flow in small vessels than in those of larger bore, contrary to current thinking.

METHODS

Blood samples were obtained from twenty-four healthy, human volunteers, by venesection, and placed into heparinized (12·5 i.u. ml^{-1}) tubes. The samples were mixed on a roller at room temperature, until used within the next 4 h. Plasma was obtained by centrifugation of the blood at 2000 *g* for 10 min. Higher haematocrits were obtained by removing a known volume of plasma, following centrifugation at 2000 *g*, from a known volume of blood, and remixing. Similarly, lower haematocrits were achieved by mixing a known volume of plasma with a given volume of blood. The packed cell volumes (PCV) were measured using a microhaematocrit centrifuge, operated at 12000 *g* for 3 min. The plasma fibrinogen level was ascertained by the thrombin clot technique of Rampling & Gaffney (1976). The erythrocyte flexibility, at room temperature, of each blood sample

was routinely measured by the packing-rate technique (Sirs, 1970). It was also estimated by calculating the intrinsic viscosity of the erythrocytes (KT), from $ln(N/\text{plasma viscosity})/\text{PCV}$, where N is the Newtonian viscosity coefficient, obtained by dividing the slope of the pressure–flow line for 3·6% NaCl by the slope over the linear section for blood flow, and multiplying by 0·731; with a tube bore of 0·5 mm and temperature of 37 °C. This derivation is consistent with the packing-rate technique, and avoids the previous error of including the anomalous viscosity contribution, which occurs when a single comparison of blood against a standard is used. All viscometry measurements were made with a modified Coulter–Harkness capillary viscometer. This was adapted to measure plasma and blood flow through different bores and lengths of capillary tubes. The tube bores were checked by measuring the length of a drop of mercury in the capillary, and weighing the drop. Four tubes were used to assess the effect of tube bore on the flow rate of blood: 0·2 mm bore and 2·1 cm length; 0·38 mm bore, 20·2 cm length; 0·5 mm bore, 20 cm length; and 0·7 mm bore, 20 cm length. The length was varied by starting with a 20 cm length of 0·5 mm precision bore tubing, which, after flow measurements had been made, was cut to a length of 14·56 cm, and the flow measurements repeated. The tube was then cut to a length of 8·52 cm, and further measurements made. The latter length was then used, in comparison with a standard 20 cm length, to obtain further data. A small modification was made to the viscometer to permit variation of the applied pressure. The capillary outlet of the mercury column was connected by pressure tubing to a plastic bottle and water manometer. By altering the volume of the bottle, using a clamp, a back-pressure acts on the mercury, so modifying the pressure the fixed displacement of the mercury applies to the viscometer tube. These differences in pressure were monitored by the water manometer. The procedure adopted was to set a given pressure difference on the water manometer, and time the flow of a fixed volume (0·188 ml) of 3·6% saline, plasma or blood through the viscometer capillary tube. When bloods from more than one individual were used, the capillary tube was flushed with 0·55 ml of 3·6% saline, between samples, to minimize possible antibody–antigen reactions. Throughout the paper, measurements of viscosity are given in units of centipoise (cP), where one poise is equal to 0·1 Pascal second (Pa s). By using three or more pressures, over the linear part of the curve, the regression coefficient, b, and the constant of the line, a, corresponding to the flow when the pressure is zero, were estimated by the method of least squares. The effective back-pressure, p, equal to $8\,lA/3\,R$, was obtained from the ratio of a/b. The error in this assessment is dependent on the errors in a and b, within the range of the pressure–flow values. The experimental data were considered acceptable when the correlation coefficient was greater than 0·99. Because the volume of the blood sample was normally restricted to 20 ml, and each viscosity measurement required 0·55 ml of fluid, there was a limit to the number of points on the line and the number of variables, of tube length, tube bore, haematocrit etc., that could be investigated during an experiment. While the above procedure established that the blood flow characteristic was linear, at high flow rates, it did not always provide a sufficiently accurate measure of p. In these circumstances the procedure was modified to make three or more measurements of blood flow at two pressure points, one high and one low, to obtain p by linear regression. Finally the experimental values of N and A were inserted into eqn (9), and the calculated pressure–flow values checked against the experimental data, as discussed later. The magnitude of A was calculated, using eqn (4), in units of $g\,s^{-2}\,cm^{-1}$. The temperature was normally maintained at $37{\cdot}3 \pm 0{\cdot}1$ °C; other temperatures were used as required.

RESULTS

A typical example of the pressure–flow characteristics of plasma and blood is shown in Fig. 1*A*. From eleven experiments, the mean value of KT, calculated from the linear section of the blood flow curve, was 2·15, with a standard deviation of 0·11. The mean value of the effective back-pressure, p, was calculated by linear regression as 2·37 cmH_2O, with a standard deviation of 0·8 cm, corresponding to A values of $1{\cdot}09 \pm 0{\cdot}37$. These values are representative of the magnitude of the parameters, but the sample is too small to assess the normal range. The effect of varying the length of the capillary tube on the magnitude of the intercept pressure, p, is shown in Fig. 2. This is consistent with eqn (4), given in the Appendix.

The anomalous viscosity coefficient A has been investigated by altering the haematocrit, the plasma fibrinogen level, the temperature and the erythrocyte flexibility. All these factors are known to modify the effect of shear rate on blood viscosity, although it should be stated these are not the only means by which this can

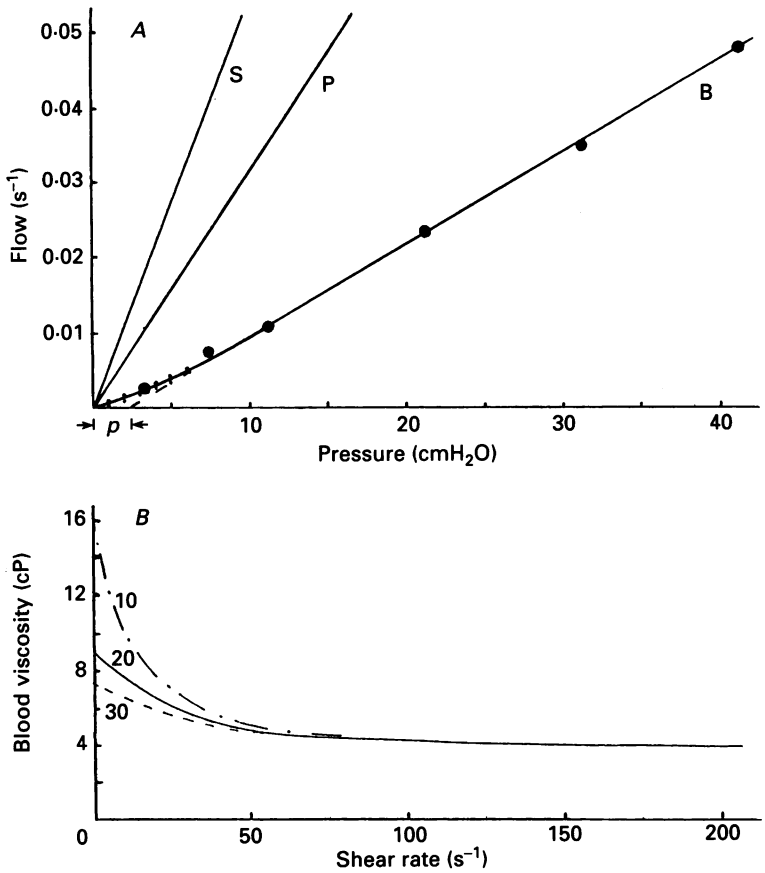

Fig. 1. A, the pressure–flow relationships for: S, 3·6% sodium chloride solution; P, plasma; B, blood at a PCV of 0·456; in a capillary tube of radius 0·025 cm and 20 cm length, at 37·3 °C. From the slope of the linear section of the blood characteristic, N = 3·255 cP. From the ratio of the constant of the line, a, to its slope, b, the pressure p is 2·65 cmH_2O, which makes A = 1·22 g s^{-2} cm^{-1}. The continuous line has been fitted using eqn (9), with N = 3·255 cP, A = 1·22 and B = 20. The upper dotted curve, at low pressures, was obtained with B = 10, and the lower dotted curve with B = 30. In panel B is shown the change of blood viscosity with shear rate, for A = 1·22, and B values of 10, 20 and 30.

be accomplished. The less well-known effect of erythrocyte flexibility was established by Chien, Usami, Dellenback & Gregersen (1967). Typical results, of more than twenty experiments, are shown in Fig. 5*A–D*. In accord with the effect of these agents on the anomalous viscosity of blood, an increase in haematocrit, plasma fibrinogen level, erythrocyte flexibility, and a decrease of temperature, increases the magnitude of p,

and hence A. Conversely, a decrease of haematocrit or erythrocyte flexibility decreases A. The effect of hypothermia, over the range 18–37·3 °C, was the subject of a separate study. At an haematocrit of 0·46, the Newtonian blood viscosity increases in an exponential manner from 3·2 cP at 37 °C, to 6·01 cP at 18·8 °C. The

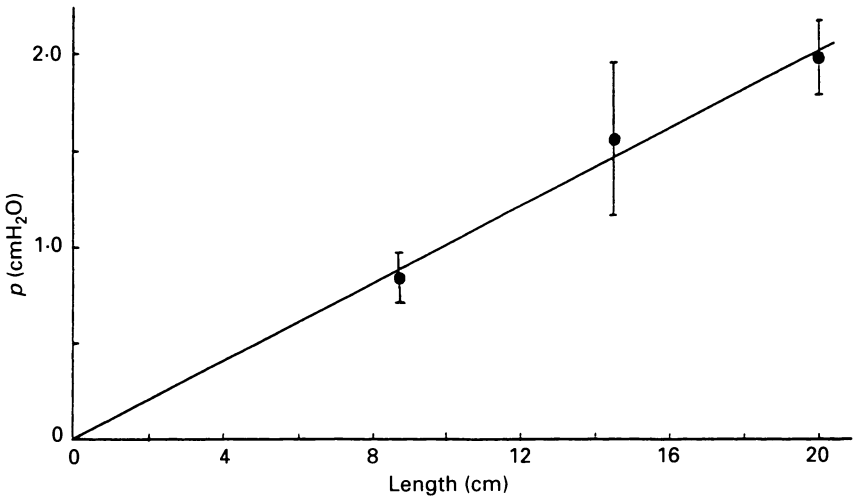

Fig. 2. The variation of the pressure p, at which the extrapolation of the linear part of the blood pressure–flow characteristic intercepts the x-axis, against length of the capillary tube. Radius 0·025 cm, temperature 37·3 °C, PCV 0·458, plasma viscosity 1·204 ± 0·021 cP, Newtonian viscosity, N, 3·151 ± 0·129, KT 2·10. The error bars represent the standard deviation.

plasma viscosity similarly rose from 1·24 to 1·99 cP. The intrinsic viscosity of the erythrocytes correspondingly increased from 2·08 to 2·39 cP, as the temperature was lowered. There was a rise of the effective back-pressure, p, from 3·2 at 37 °C to 3·84 cmH_2O at 18·8 °C, corresponding to a change of A from 1·47 to 1·76. This behaviour is unusual, in that the anomalous viscosity coefficient, A, is increased at the same time as the erythrocyte flexibility decreases.

Similar experimental measurements have been made using capillary tubes of different bore. However, in order to keep the flow rate in the linear range of the pressure–flow relationship, it was necessary to use tubes of different length, and apply a correction proportional to the length of the tube to obtain the values of p at a length of 20 cm. Three of the pressure–flow lines are shown in Fig. 4. From these data the variations of p, N and A with radius have been calculated using linear regression, and the results are shown in Fig. 5. It is quite clear that the significance of the anomalous viscosity of blood increases as the vessel bore decreases. This would be the case if A were constant, but the results indicate that A increases with decrease of vessel bore, which further flattens the velocity profile and decreases flow. The Newtonian viscosity N decreases in smaller bore tubes, in accord with the Fahraeus–Lindqvist effect.

DISCUSSION

The pressure–flow curve for blood, in Fig. 1*A*, is qualitatively in agreement with numerous earlier data. Although at higher flow rates the change of blood flow with pressure is linear, the extrapolation of the linear section to zero flow does not pass

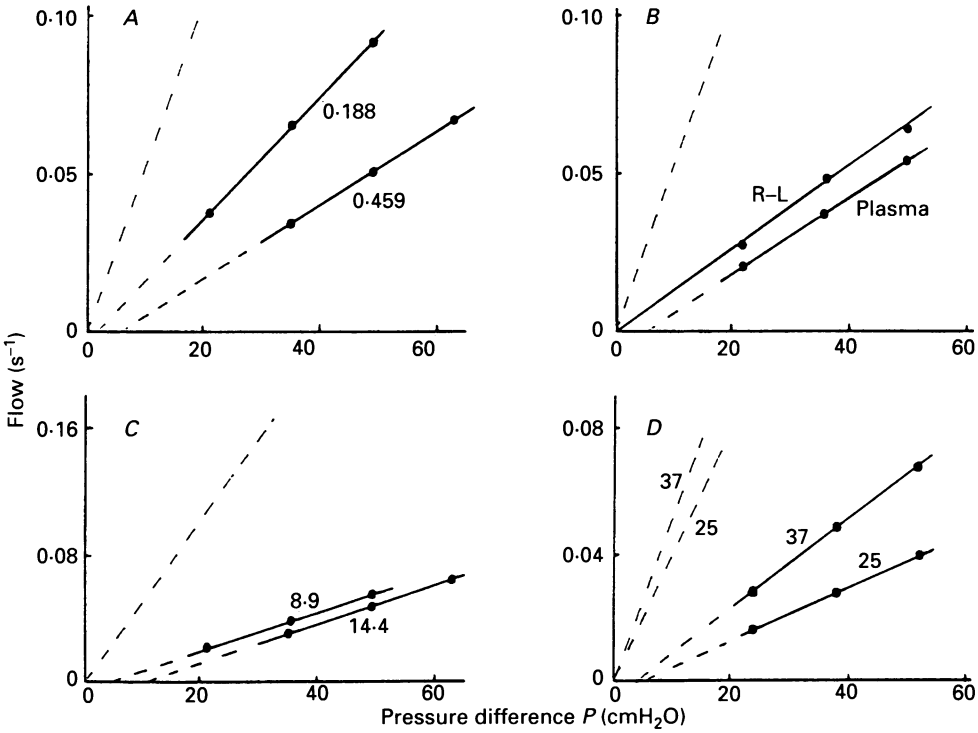

Fig. 3. The effect on the pressure–flow curves of blood, and magnitude of p, of haematocrit, fibrinogen level, erythrocyte flexibility and temperature; in a capillary tube of 0·025 cm radius. The dashed line on each diagram is for 3·6 % sodium chloride. *A*, the effect of changing the PCV from 0·188 to 0·459 at 37·3 °C. *B*, erythrocytes, at a PCV of 0·47, suspended in Ringer–Locke solution (zero fibrinogen, and KT = 3·03) and in plasma (fibrinogen 2·37 mg ml^{-1}, KT = 2·13). Note that the flow of cells in Ringer–Locke solution is predominantly Newtonian. *C*, the effect, at a PCV of 0·45 and temperature of 37·3 °C, when the erythrocyte flexibility is varied from a packing rate of 8·9 % min^{-1} (fibrinogen level 5·74 mg ml^{-1}) to 14·4 % min^{-1} (fibrinogen level 6·16 mg ml^{-1}). *D*, the effect of a change of temperature, from 25 to 37·3 °C, at a PCV of 0·448 and a fibrinogen level of 2·91 mg ml^{-1}.

through zero pressure. This implies, under these conditions, and unlike plasma, that blood cannot be regarded as a Newtonian fluid at any flow rate. The constants N, A and B in eqn (5) of the Appendix are obtained in the following way. The value of N is calculated, as explained in the Methods section, from the slope of the linear portion of the curve; this gave a value of 3·255 cP. Next an estimate of A is obtained from the value of the effective back-pressure, p, as given by eqn (4). Inserting the known values of l and R, the value of A was found to be 1·22. Now using a computer program of eqn (9), it proved relatively quick to obtain the value of B required to fit

the whole curve. In the process the values of A and N may need small adjustment to obtain the best fit. The linear section of the curve, and to a lesser extent the flow at low pressures, is insensitive to the magnitude of the constant, B. In Fig. 1B is plotted the change of viscosity with shear rate, when B is varied from 10 to 20, then 30. This

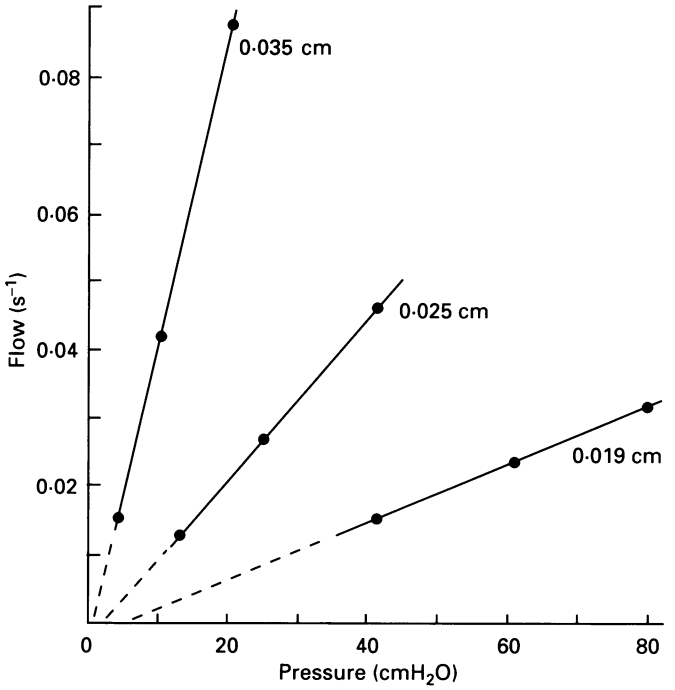

Fig. 4. The effect of changing the tube radius from 0·035, 0·025 to 0·019 cm, on the pressure–flow characteristic of blood. Temperature 37·3 °C, PCV 0·442.

range of values has negligible effect on the calculated flow–pressure curve at higher pressures, and only marginal effect, to the extent that all three curves in Fig. 1A are within the experimental errors, at low flow rates. Thus it is not possible to accurately ascertain the magnitude of B using capillary viscometry, but, more important, it is of little consequence anyway in the interpretation of *in vivo* blood flow, which is normally on the linear part of the curve. It is the magnitude of A that matters, which relates to the anomalous viscosity component of the blood at shear rates above approximately 30 s^{-1}. This simplifies the investigations necessary to interpret blood flow, and eqns (3) and (4) can be applied, as a first approximation, to explain the majority of *in vivo* phenomena. Physically *in vivo* blood flow can be represented by a line, whose slope is N, and the intercept with the x-axis is proportional to A. So varying A will shift the line to the left or right, while, if N is constant, retaining the same slope.

It is worth looking further at the physical basis of this interpretation, which is related to the velocity profile of blood flow. This aspect becomes particularly important in explaining how the anomalous viscosity component interacts with the Fahraeus–Lindqvist effect. A similar integration to that described in the Appendix

can be used to obtain the variation of the velocity of blood flow over the vessel cross-section. Three separate situations are shown in Fig. 6*A*: the parabolic velocity profile for Newtonian flow; the flattened profile of a Bingham plastic, as governed by eqn (1); and two curves corresponding to eqn (5). It can be seen that there is a marked

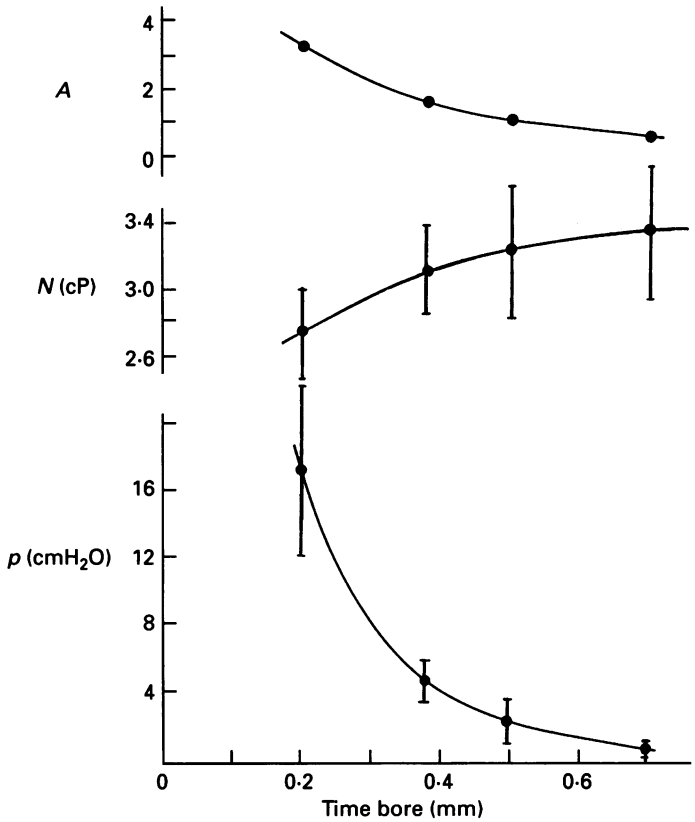

Fig. 5. Values of the anomalous viscosity coefficient A, the Newtonian viscosity component N, and the pressure p, at different tube bores. Data from Fig. 4 were used. Tube length 20 cm. The error bars represent the 95% confidence limits, estimated by linear regression.

change in the velocity from Poiseuille flow ($A = 0$ or $B =$ infinity), to that using eqn (1) ($A = 1{\cdot}22$ and $B = 0$), where the profile is flattened. When $A = 1{\cdot}22$ and $B = 20 \pm 10$, the main part of the profile, relative to that for $A = 1{\cdot}22$ and $B = 0$, is unchanged; all that happens is that the flattened segment is now slightly curved. The increase of flow, occasioned by the increase in area under the curve, can be neglected. The difference does, however, become significant at slow flow rates. By contrast, a small increase in A, as indicated by the interrupted curve, further blunts the velocity profile. If A, and the other parameters, are kept constant, as R is decreased, the profile is progressively blunted, consistent with the *in vivo* observations of Gaetghens, Wayland & Meiselman (1971). Closer analysis of the curves in Fig. 6*A* reveals that they are effectively parabolic. The highest flow is obtained with Newtonian flow

($A = 0$), and $N = 3{\cdot}225$ cP. The curve for $A = 1{\cdot}22$, $B = 20$ fits a parabolic profile, $r = 0{\cdot}9998$, with an effective Newtonian viscosity of 3·65 cP. The curve for $A = 2$ fits a parabolic velocity profile, $r = 0{\cdot}998$, with a viscosity of 3·96 cP. This means the velocity profile does not provide adequate evidence that blood flow is Newtonian in

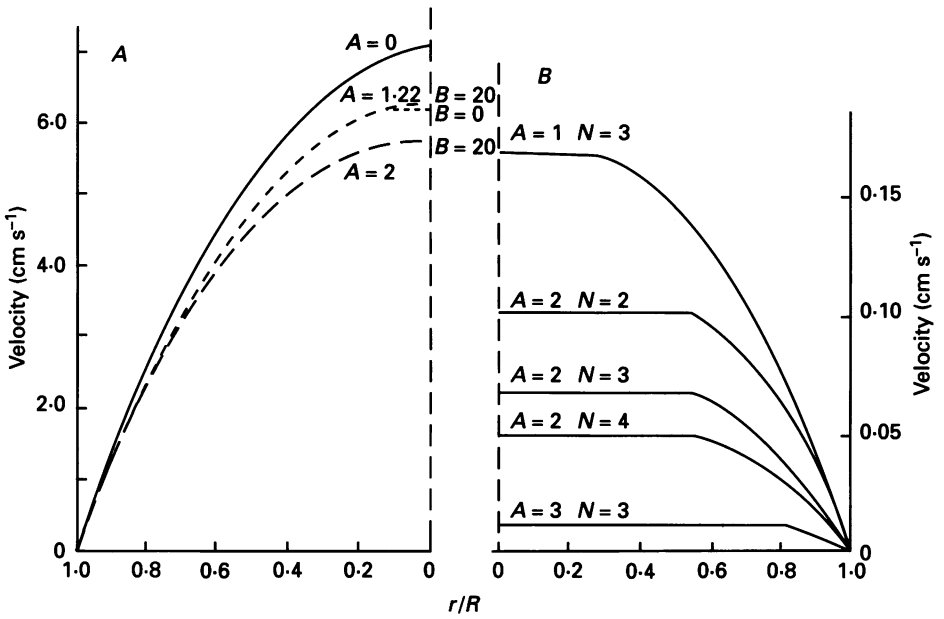

Fig. 6. *A*, the variations of the velocity profile, at an applied pressure of 30 cmH_2O, for blood with a Newtonian viscosity component, N, of 3·255 cP, in a capillary tube of 0·025 cm radius: when $A = 0$, Poiseuille flow; $A = 1{\cdot}22$, $B = 20$, and for comparison of the effect (dotted line) when $A = 1{\cdot}22$ and $B = 0$; and when $A = 2$ and $B = 20$; *B*, the effect of the Newtonian viscosity, N, and anomalous viscosity component, A, on the velocity profile of blood flowing through a capillary tube of 0·01 cm bore and 20 cm length, with an applied pressure of 30 cmH_2O; assuming the viscosity is given by eqn (1).

smaller vessels. If we consider blood flow over the linear section of the pressure–flow characteristic, then to a first approximation we can neglect the effect of B, and the velocity profiles reflect the influence of A and N. This is shown in Fig. 6*B*. The Newtonian viscosity component, N, determines flow in the fluid layer adjacent to the vessel wall, while A controls the diameter of the flattened core. As A is increased, with N constant, the flow rate falls. A change of A has a greater effect when N is small. If A is constant, and N changed, the diameter of the flattened core remains the same, as the flow changes. It can also be seen that a significant change of flow can occur without change of shear rate at the vessel wall. Thus a high shear rate at a vessel wall does not necessarily mean that the flow is Newtonian. The simple and effective way to establish if the flow is non-Newtonian, is to ascertain whether or not the change of blood flow with pressure rises linearly from zero pressure, or is of the form shown in Fig. 1*A*.

Figure 3*A* shows that an increase of the haematocrit increases A, and vice versa. The data of Haynes and Burton show that the linear part of the pressure–flow

curves, at different haematocrits, extrapolate to the same intercept on the flow axis. Since the Newtonian viscosity increases exponentially with haematocrit, this implies that the magnitude of A increases exponentially with haematocrit. The data in Fig. 3 indicate that A increases threefold, in changing the haematocrit from 0·188 to 0·459. At a comparable tube bore, but at a temperature of 25·5 °C and with human erythrocytes suspended in acid citrate dextrose solution, both factors that reduce erythrocyte flexibility, the corresponding increase observed by Haynes and Burton was twofold. Their value of A, at a PCV of 0·55 in a 57·04 μm tube, was 7·7. The adverse effect of a high haematocrit in newborn infants is offset by a decreased flexibility of fetal erythrocytes (Sirs, Lissauer & Rivers, 1987). Erythrocyte flexibility is linked to the fibrinogen concentration. The line in Fig. 3*B*, for cells in Ringer–Locke solution, suggests that in these circumstances the erythrocytes are relatively inflexible, and A approaches zero. A change of the erythrocyte flexibility, from a packing rate of 9·8 to 14·4 % min^{-1}, increases A by a factor of two. Thus the concept that an increase of erythrocyte flexibility automatically improves blood flow is untenable. The comprehensive data of Kemble & Hickman (1972), on the effect of fibrinogen on blood and plasma viscosity, can be used to estimate the effect of fibrinogen on A, at high shear rates, utilizing eqn (1). The calculated value of KT, at a fibrinogen level of 3 mg ml^{-1}, is 2·3, which is in the upper range of the previous values, probably because they used EDTA. None the less, there is a linear decrease of KT, from 2·46 to 1·95, and linear increase of A by a factor of 1·42, when the fibrinogen concentration rises from zero to 9 mg ml^{-1}. High fibrinogen levels have been implicated in cardiovascular disease. In some adult diabetics, the erythrocyte flexibility is decreased, relative to that expected for the patient's fibrinogen level, by an unknown factor, and may even be maintained in the normal range (Sirs, Boroda & Rampling, 1981). This has the effect of counterbalancing the adverse effect of fibrinogen on the anomalous viscosity coefficient A. The effect of hypothermia on blood rheology is even more detrimental. The Newtonian viscosity, N, increases, due to an increase of plasma viscosity and decrease of erythrocyte flexibility. The anomalous viscosity coefficient, A, also increases, although this is less than might have been the case if the erythrocyte flexibility had not decreased. Overall, these studies suggest there is an optimum balance of erythrocyte flexibility, haematocrit and fibrinogen level. When the erythrocyte flexibility is below this optimum, the Newtonian component increases, decreasing blood flow. When the erythrocyte flexibility is high, A increases, again decreasing blood flow.

The Newtonian viscosity, N, decreases and A increases, with decrease of tube bore. This is probably due to the movement of cells from the region of high shear rate at the vessel wall into the central core. A change of the anomalous viscosity coefficient will modify the apparent vessel haematocrit. When A is large, the mean flow velocity of the cells will be reduced, relative to the mean flow rate of plasma, and, in accord with the Fahraeus effect, the apparent vessel haematocrit will rise. A high value of A will also reduce the thickness of the layer at the vessel wall, so reducing plasma skimming at bifurcations. The data of Haynes and Burton also show an increase of p, and hence of A, with reduction of radius, similar to the data shown in Fig. 5. The smallest radius used by Haynes and Burton was 57·04 μm, and, at an haematocrit of 0·45, the calculated value of A is 6·3. The pressure–flow curves for blood flow through micropore filters with 6·8 μm pores, obtained by Gregersen, Bryant, Hammerle,

Usami & Chien (1967), are qualitatively the same as in Fig. 1*A*. The magnitude of A, calculated from these data, is of the order 100. This high value is likely to be due to an underestimate of the effective path length, quoted as being 13 μm. Whittaker and Winton also observed that the linear range of blood flow through the hindlimb of the dog did not extrapolate to zero flow at zero pressure. By a control experiment they established that this effect was due 'to a property of blood itself'. The magnitudes of p, as shown in their Fig. 6, are higher than the values shown in Fig. 5, consistent with p continuing to increase as R falls, and exponentially increase with PCV ($r = 0{\cdot}994$). They calculated blood viscosity values by comparing the flow rate at a single high pressure, against the flow rate of a known standard. The procedure adopted reflected changes of N. Their values of blood viscosity, at a PCV of 0·48, were 2·05, 2·15 and 2·25, which compare with the value of N, estimated from the slope, of 1·96 cP. Similarly at a PCV of 0·83, the direct method gave 4·84 cP, while the slope gives 3·69 cP. The nature of blood flow in the hindlimb of the dog supports the earlier conclusion that the anomalous viscosity component of blood has a direct influence on blood flow through the microcirculation. The magnitude of A cannot be determined from the values of p, because it requires a knowledge of the equivalent length and bore of the blood vessels. There is, however, another factor that Whittaker and Winton did not take into account. Prior to their experiments they defibrinated the blood, which reduces the magnitude of A. It is not possible to estimate the consequences of this procedure, from the limited data available on the rheological properties of dog's blood. At an haematocrit of 0·49, the flow through the limb is slower than would occur with a Newtonian fluid of viscosity 4 cP, up to a pressure of about 22 mmHg. Above this pressure the limb flow is higher, and steadily increases with pressure, relative to Newtonian flow. If the PCV is increased, the pressure at which the cross-over occurs is increased. It is the cross-over phenomenon that accounts for the disagreement regarding the effect of tube bore on the viscosity of blood. The data of Denning & Watson (1906), where, with a high cell count, they found more than a fivefold increase in viscosity as the tube bore was decreased from 3·5 to 0·6 mm, were obtained using horse blood, with a driving pressure of about 20 cmH_2O. We now know that horses have very flexible erythrocytes (Amin & Sirs, 1985), and a high anomalous viscosity. The results of Denning and Watson are consistent with what occurs below the cross-over pressure. It raises, however, another issue, that animal models of the human circulation are only valid when the rheological properties of the bloods are comparable.

To a first approximation, in terms of eqn (3), the effect of the anomalous viscosity component is as though there is an effective back-pressure p, reducing the flow. The magnitude of p increases as the radius, R, is reduced, and so will have the greatest effect in small vessels where the pressure gradient P is low, in the venules and in the lungs. There is, however, another way of looking at the adverse effects of the anomalous viscosity component. If, corresponding to the use of the Poiseuille relationship, we consider blood flow can be algebraically represented by:

$$Q = kPR^n, \tag{10}$$

where k is a constant, and n the power to which the radius is raised, we can, for a given pressure gradient, plot:

$$\log Q = \log kP + n \log R, \tag{11}$$

and obtain n from the slope. The experimental data of the effect of the radius of the capillary tube on values of N and A, shown in Fig. 5, were used, assuming a value for B of 20 to calculate the flow, with a vessel length of 1 cm, at varying radii and pressures, using eqn (9). The values of $\log Q$ and $\log R$ were then calculated, for

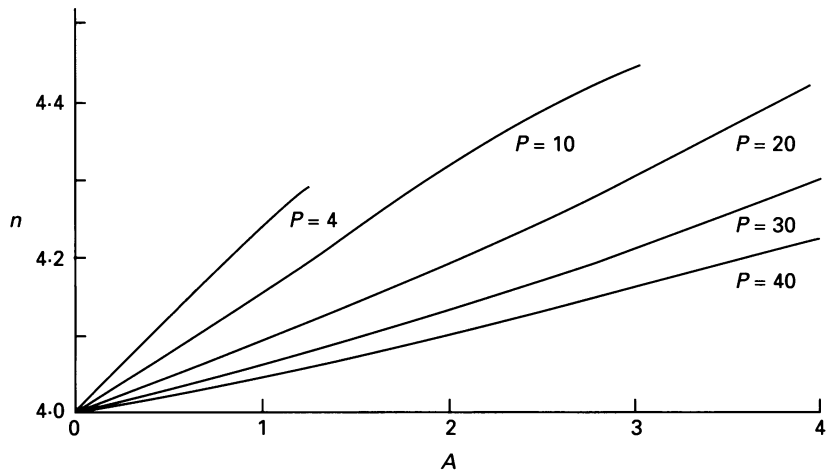

Fig. 7. Calculated values, using eqns (9) and (11), of the power to which the radius is raised, n, in eqn (10), following variation of A. The applied pressure, P, indicated on each curve is in cmH_2O. $N = 3{\cdot}25$ cP, $B = 20$ and $l = 20$ cm.

pressures of 1, 5 and 10 cmH_2O. The points were fitted by linear regression analysis. All the lines had correlation coefficient, greater than 0·999, and, from the slopes, the respective values of n were 4·85, 4·62 and 4·14. These values are greater than 4, as applies to Newtonian fluids, and increase as the pressure is lowered. To obtain independent confirmation of this conclusion, the flow values at varying radii, and at a pressure of 5 mmH_2O per cm length, were obtained from the data of Haynes and Burton, and plotted on a logarithmic scale. A line is obtained with a correlation coefficient of 0·98, and a value of n of 4·75. This is for blood at a haematocrit of 0·45, and at a temperature of 25·5 °C. To obtain a quantitative estimation of the interaction of the various factors that influence the power to which the radius of the vessel is raised, n, incremental values of A and P, at varying radii R, with a vessel length of 1 cm, and N constant, were used to calculate Q, using eqn (9). The corresponding values of n were calculated by eqn (11). The results are shown graphically in Fig. 7. An increase of A produces a proportionate increase of n. A decrease of P, with A constant, also increases n. The change of blood flow following an increase or decrease of the vessel radius is interlinked with the anomalous viscosity of blood. This in turn depends on the haematocrit, fibrinogen level, erythrocyte flexibility and temperature. Not only is the peripheral resistance modified, but the degree of change of blood flow for a given change of radius is altered, which will affect vasomotor control. A similar analysis was undertaken using values appropriate to the data of Whittaker and Winton. At a pressure of 80 mmHg, the value of n, with $A = 10$, is 4·08, and with $A = 15$, $n = 4{\cdot}13$.

The overall conclusion of the experimental and theoretical investigations outlined in this paper is that, contrary to current thinking, the anomalous viscosity component of blood has a major influence on flow through the microcirculation.

APPENDIX

An explanation for the linear range of the pressure–flow characteristic, in Fig. 1*A*, was derived by Buckingham (1931), on the basis that blood viscosity can be considered as the sum of a Newtonian and a non-Newtonian component, of the form:

$$\eta = N + A/D, \tag{1}$$

where η is the total viscosity, N the magnitude of the Newtonian component, A the anomalous viscosity coefficient and D the shear rate. When this is used, instead of η being constant as in the Hagen–Poiseuille derivation, the change of blood flow with pressure becomes:

$$Q = \frac{\pi P R^4}{8Nl} - \frac{\pi A R^3}{3N} + \frac{2\pi A^4 l^3}{3NP^3}, \tag{2}$$

where Q is the flow rate, P the pressure between two points on the tube, l is the distance apart, and R the radius of the capillary tube. Putting in values obtained from the linear portion of the curve in Fig. 1*A*, its slope gives N and the value of the pressure at zero flow rate A. For $P = 30$ cmH_2O, $R = 0{\cdot}025$ cm, $l = 20$ cm, $N = 3{\cdot}255$ cP and $A = 1{\cdot}22$, from left to right the magnitude of the individual terms are $6{\cdot}93 \times 10^{-3}$, $6{\cdot}13 \times 10^{-4}$ and $4{\cdot}47 \times 10^{-8}$. At higher pressures we can neglect the last term, and eqn (2) simplifies to:

$$Q = \frac{\pi R^4}{8Nl}(P - p), \tag{3}$$

where:

$$p = \frac{8lA}{3R}. \tag{4}$$

It is apparent that this only partially explains the non-Newtonian behaviour of blood flow, since it would require a pressure p to be applied before flow would start. However, with the experimental data there is an initial slow increase of blood flow, from zero pressure. Physically this difference arises because as the flow gets slower, and D falls, the term A/D in eqn (1) increases to infinity. It is necessary to include a further constant, B, to keep the overall viscosity finite at low shear rates, by modifying eqn (1) to:

$$\eta = N + A/(B + D), \tag{5}$$

where B is small relative to D at higher flow rates. We proceed, as in the derivation of the Hagen–Poiseuille equation, by equating the force applied to the end of a cylindrical section of fluid, of radius r, to the viscous resistance offered over the surface area of a cylinder. Algebraically this is expressed as:

$$P\pi r^2 = (2\pi rl)D\eta. \tag{6}$$

Then substituting for η, from eqn (5), and rearranging:

$$\frac{dv}{dr} = -\left(\frac{(Pr/2l)-(BN+A)}{2N}\right) - \sqrt{\frac{BA}{N}}\sqrt{1+\frac{((Pr/2l)+(NB-A))^2}{4NBA}}. \tag{7}$$

The variation of velocity, v, with radius can be obtained by integrating eqn (7), and then the flow rate, Q, from the integral of $(2\pi r)v\,dr$. Since v is zero at the wall, when $r = R$, it is simpler to calculate Q directly from:

$$Q = -\int_0^R \pi r^2 \frac{dv}{dr} dr. \tag{8}$$

Equation (8) can be integrated, by substitution of elementary transcendental functions, to give:

$$\left.\begin{aligned} Q = {} & (\pi/2N)[(PR^4/8l)-(WR^3/3)] \\ & +(4\pi FHEZ^2)[(KG/E)-(ZJ/E)+\log((G/E)+K)-\log((Z/E)+J)] \\ & +(5{\cdot}333\,\pi FHZD)[(J^3-K^3)] \\ & +(\pi FHDE)[K(2(G/E)^3+(G/E))-J(2(Z/E)^3+(Z/E)) \\ & +\log((Z/E)+J)-\log((G/E)+K)], \end{aligned}\right\} \tag{9}$$

where

$$Z = BN-A; \quad W = BN+A; \quad D = 4NAB; \quad E = \sqrt{4NAB}; \quad F = \sqrt{AB/N};$$
$$G = (PR/2l)+Z; \quad H = l^3/P^3; \quad J = \sqrt{1+(Z^2/D)}; \quad K = \sqrt{1+(G^2/D)}.$$

This is the pressure–flow relationship that should be used to interpret blood flow. The equation has been written as a simple computer program, so that it is only necessary to specify the initial parameters of length, radius, Newtonian viscosity, A and B to obtain the values of flow for a given pressure.

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