Eye (1991) **5**, 151–158

Blood Rheology and Ischaemia

G. B. NASH
Birmingham

Summary
Ischaemia is essentially the failure of tissue to obtain a sufficient oxygen supply for its function. In the context of rheology, which is the study of the deformation and flow of materials, this implies failure to deliver the blood, rather than failure to oxygenate the blood or extract oxygen from it. Resistance to the delivery of blood is generally considered to have vascular and rheological components. Vascular effects on resistance may often be dominant, and there is wide appreciation of the ischaemic consequences of vascular obstruction and narrowing, for example in atherosclerotic disease. However, rheological factors can vary widely between individuals and in disease, and such variations have the potential to influence oxygen supply.[1,2] Here, the rheological factors which affect blood flow are reviewed and their role in the development of ischaemia is discussed, with particular reference to the eye where possible.

Rheological Factors Affecting Blood Flow

The rheological properties of the blood can conveniently be divided into bulk properties and cellular properties (Table I). Broadly speaking, the bulk properties (blood viscosity and its determinants) dominate flow in large vessels, whereas cellular factors have greater influence in microvessels with diameters of the order of the cellular dimensions. At the level of the microcirculation it may not be appropriate to consider the viscosity of the blood as a continuum, but may be better to consider separately the flow properties of the cellular constituents and the plasma.

Table I. *Rheological properties of the blood and their major determining factors*

Bulk Properties	→Flow resistance in large vessels	
Factors:		
Blood Viscosity		Haematocrit
		Plasma Viscosity
		Red Cell Aggregation
		Red Cell Deformation
Cellular Properties	→Resistance to capillary entry and obstruction of microvessels	
Factors:		
Red Cell Deformability		Intrinsic Structure
Red Cell Adhesiveness		Plasma Factors
White Cell Deformability		Intrinsic Structure
White Cell Adhesiveness		Functional State (Activation)
		Plasma Factors

From: Department of Haematology, The Medical School, University of Birmingham, Birmingham B15 2TT.

Correspondence to: Dr. G. B. Nash, Department of Haematology, The Medical School, Vincent Drive, Birmingham B15 2TT.

Bulk Properties

Blood viscosity is determined by haematocrit (and leukocrit in some hyper-leukocytic states), plasma viscosity and red cell aggregation (which occurs at low shear rates). The ability of the red blood cells to deform and align in flow greatly reduces the viscosity of the blood from the level it would be if these cells were non-deformable, but there are few, if any, clinical conditions where abnormal deformability has a significant affect on bulk viscosity. The most marked abnormalities in red cell mechanics are generally linked with anaemia, which has a greater effect on bulk viscosity than impaired red cell deformability.

Haematocrit

The relationship between blood viscosity and haematocrit is logarithmic. For example, at low shear rate ($1s^{-1}$) blood viscosity varies from about 13 to 45 mPa.s for haematocrit varying from 0.3 to 0.5, and at a higher shear rate ($100s^{-1}$) from 3.6 to 6.4 mPa.s. The dependence on shear rate arises mainly from the effects of red cell aggregation (see below), but alignment, deformation and close packing of red cells also reduces viscosity as the shear rate increases. Increasing haematocrit increases the oxygen carrying capacity of the blood, and the quotient of haematocrit/viscosity may be used as a parameter to describe rate of oxygen transport.[1] This parameter gives a bell shape curve when plotted against haematocrit, with optimal transport in the haematocrit region of 0.3 to 0.5.

The normal range of haematocrit is quite wide, so that the range of viscosities is even wider. It seems that for changes in viscosity *per se* to cause ischaemic problems in the eye, haematocrit must rise above 0.5.[3] In this polycythaemic region there are typical pathological manifestations of retinal vein dilation, central retinal vein thrombosis and congestion of conjunctival venules.[4] The mechanism seems to be directly rheological, with increased viscosity causing increased flow resistance, and symptoms which respond to treatment which lowers haematocrit. Anaemia is also associated with abnormalities in the ocular circulation.[5] This is probably not of rheological origin, except possibly when it is associated with abnormalities in the red cells themselves (see below).

Plasma Viscosity

Variations in the viscosity of plasma depend on variations in its protein constituents. In normal plasma, the main contributions are from globulins, albumin and fibrinogen, in that order, and there exists a relatively narrow normal range of viscosities (Table II).[6] Plasma viscosity is raised in a vast range of acute and chronic infections, and most degenerative and neoplastic diseases.[6] The changes depend mainly on elevation of fibrinogen and have quite small though easily detectable effects on plasma viscosity. They may, however, have greater effects on red cell aggregation (see below). On the other hand, paraproteinaemia associated with myeloma and Waldenstrom's disease can have very marked effects on plasma and blood viscosity and can directly lead to hyperviscosity syndromes.[7,8] Macroglobulinaemia, for example, can raise plasma viscosity by several hundred percent.[6] These rheological changes lead directly to ocular problems (dilation of retinal veins, constriction at arterio-venous crossings and retinal haemorrhages) which are reversible by viscosity lowering therapy such as plasmapherisis.[4,8]

Red Cell Aggregation

Blood viscosity rises sharply as the shear rate is lowered, for example increasing about five-fold in normal blood when the shear rate decreases from 100 to 1 s^{-1}. This phenomenon is chiefly caused by reversible red cell aggregation. Deformation and alignment of red cells with increasing shear rate makes a lesser contribution to viscosity reduction. Red cell aggregation can be most easily observed at

Table II. *Plasma Viscosity: determinants and values in health and disease*

Normal	1.5 to 1.72 mPa.s (at 25°C)
Albumin : Globulin : Fibrinogen	
Plasma content	4.0 : 2.5 : 0.3
Contribution to viscosity	36 : 41 : 22
Acute and Chronic Disease	
Malignancy	1.7 to 3.3 mPa.s (at 25°C)
Paraproteinaemia	
Myeloma	Typically>3 mPa.s (at 25°C)
Waldenstrom's Macroglobulinaemia	Up to 10–20 mPa.s (at 25°C)

Data from Harkness.[6]

stasis where cells are seen to form long stacks of cells or rouleaux. Shearing of the blood disrupts these large scale structures, although low shear rates may actually accelerate initial formation of aggregates.[9] Aggregation is generally attributed to the ability of absorbed large proteins to form cross-bridges between cell membranes. Recent theories have suggested that there may also be colloid osmotic forces resulting from a layer depleted of protein between adjacent cellsurfaces.[10] Whatever the mechanism, aggregation in whole blood is caused mainly by fibrinogen, with lesser contributions from γ-macroglobulin and immunoglobulins.[11] Thus, aggregation will be elevated in most conditions in which plasma viscosity rises, and this is the basis for the commonly used erythrocyte sedimentation rate (ESR) test. The effects on viscosity may be quite pronounced at low shear rates.

Two contributions to ischaemia can be envisaged. First, increased aggregation may directly elevate blood viscosity in diseases associated with raised fibrinogen. Second, if flow rate is reduced for some other reason (e.g. vascular obstruction) then viscosity of otherwise normal blood will rise locally. Because of the dependence on shear rate, aggregation will have most effect on viscosity in the venous circulation where shear rates are at their lowest. Flow into microvessels could also be impeded by aggregates if they were present on the arterial side. Estimates of shear rates *in vivo* in animal circulations generally do not fall below $100\,s^{-1}$ in any region.[12] However, in any large vessel the shear rate is low in the centre and high at the periphery so that aggregates may form where average shear rates are quite high. For example, by ultrasound echogenicity, aggregation has been demonstrated to exist in large veins in humans.[13]

In low flow states, viscosity will rise sharply. If stasis occurs intermittently, red cell aggregation may give rise to a yield stress which must be overcome before flow can be restarted.[14] Nevertheless, the effect of aggregation on blood flow remains controversial, and it has been demonstrated that flow in tubes can actually be facilitated by aggregate formation and migration of cells to the centre line, because of formation of a lubricating, cell-depleted layer near the wall.[15] It is probably true to say that any contribution of aggregation to ischaemia will be most marked when other pre-disposing factors are present, such as vascular occlusion and reduced perfusion pressure. With respect to the eye, a number of systemic illnesses associated with retinal ischaemia (e.g. diabetes and rheumatic disease) will be accompanied by elevated fibrinogen and hence aggregation. More specifically, retinal vein occlusion has been shown to be accompanied by increased aggregation and blood viscosity, only partially explainable by elevation of fibrinogen.[16,17]

Cellular Properties

Red Cell Deformability

The red blood cell is able to undergo repeated, reversible shape changes in the circulation, and indeed this is an essential requirement if it is to pass through narrow capillaries. This deformability depends on the cell's structure: its geometry, membrane viscoelasticity and cytoplasmic viscosity. The red cell has excess surface area over that required to encapsulate its volume, and this is essential to allow shape transformation without change in surface area. The membrane in fact will allow very little area dilation before rupture, and so deformation occurs at essentially constant area. Resistance to deformation and rate of deformation are primarily determined by the membrane's intrinsic rigidity (shear and bending elastic moduli) and viscosity. Internal cytoplasmic viscosity will also affect rate of deformation under certain circumstances (particularly during bending rather than shearing), although this viscosity can become so elevated upon dehydration or haemoglobin polymerisation that it becomes a dominant factor. In principle, abnormalities in any of the above-mentioned factors can compromise ability to circulate and could contribute to ischaemia.

In practice, marked abnormalities in red cell deformability are quite rare. In sickle cell disease the oxygenated cells include a subpopulation of dense, viscous and rigid cells.[18] Upon deoxygenation, polymerisation of haemoglobin S occurs and the internal viscosity rises by several orders of magnitude, with consequent dramatic further loss of deform-

ability.[19,20] Ischaemic complications occur, gradually leading to damage to the major organs, including the eye. In no other disorder is there convincing evidence of a red cell mechanical abnormality being a primary cause of ischaemia. Genetic defects of membrane structure can lead to loss of membrane stability and deformability, loss of membrane area and changes in cell shape; these are poorly tolerated and can lead to haemolytic anaemia.[21] Although haemolytic anaemia is associated with ischaemic optical complications, the mechanism may not be rheological.[22] Ovalocytosis is quite common in Melanesia, and this genetic variant is associated with a several fold increase in membrane rigidity.[23] No ischaemic complications have been described. Abnormal filterability of red cells has been found in diabetics (see, e.g. Stuart and Juhan-Vague[24] for review). The defect is quite mild and apparently only occurs in those with poorly controlled disease. Its contribution to ocular complications is doubtful.

Red Cell Adhesiveness

In vitro, normal red cells show a slight tendency to adhere to cultured endothelium. This phenomenon has not been demonstrated *in vivo,* except for sickle cells transfused into animal models[25] and in falciparum malaria.[26] In malaria, the adhesiveness develops at a certain stage of parasite maturation, is mediated by specific endothelial cell receptors, and is thought to play a key role in ischaemic complications.[27] Sickle cells have increased adhesiveness judged by *in vitro* assays, and plasma factors as well as cellular ones may be involved.[28,29] Increased adhesion has also been observed in diabetes,[30] after myocardial infarction,[31] and in systemic sclerosis.[32] In these disorders, plasma proteins increased adhesion, and it might be that the acute phase response is quite generally associated with increased plasma-mediated adhesiveness. This hypothesis remains to be tested. Outside of malaria, the effect of adhesion on circulatory pathology is uncertain.

White Blood Cell Mechanics, Adhesiveness and Activation

White blood cells are much more resistant to deformation than red cells (see Table III for some comparative properties). White cells have sufficient excess surface area in the form of surface folds, and probably a quite flexible membrane, but their internal viscosity is several orders of magnitude higher than that of red cells.[33,34] Although outnumbered by about 700:1 in the normal circulation, they probably contribute appreciably to flow resistance at the capillary level. In the normally functioning human microcirculation, for example, white cells have been observed to cause intermittent capillary blockage.[37] In experimental animal studies, an induced drop in perfusion pressure has been found greatly to exaggerate this phenomenon and lead to impaired flow even upon reperfusion.[38,39]

The most important factor in ischaemia is probably the reactive nature of the white cells, and particualrly neutrophils. Activation is associated with marked increases in rigidity and adhesiveness.[34,40,41] A proportion of unstimulated neutrophils are typically marginated (rolling slowly along venular walls) but this margination increases and cells become firmly attached if activated. This adhesion can lead directly to vascular obstruction and increase in flow resistance.[42]

There may thus be a rheologically based contribution of neutrophils to ischaemia. Acute or chronic reduction of perfusion pressure could lead to vascular obstruction if the driving force is insufficient to force these cells through capillaries. Trapped cells may become activated and initiate a process of tissue damage by releasing reactive oxygen metabolites and lytic enzymes.[43] This would cause further release of activating factors and newly arriving cells would become rigidified and adhesive.

This presupposes a vascular initiating factor, although another possibility is that inflammatory changes or infection could lead to neutrophil activation. In general, changes induced by activation in one region, e.g. an ischaemic limb, could lead to neutrophil entrapment in other organs, mediated by plasma born activating factors.

The involvement of white cells in ischaemia in the eye has received little attention, except in leukaemic states.[44,45] In general, hyperleukotic states have compensatory anaemia, so

Table III. *Comparative Mechanical properties of red and white blood cells*

Geometry	*Red Cells*	*White Cells*
Shape	Discoidal	Spherical
Diameter	~ 8um	~ 8um
Volume	~ 90fl	200–300fl
Surface Area	~ 135um^2	300–400um^2
Excess Surface Area	~ 40%	~ 100%
Membrane viscoelasticity		
Shear rigidity	~ 10^{-5} N.m^{-1}	
Bending Rigidity	~ 10^{-19} N.m	Unknown
Viscosity	~ 10^{-6} N.s.m^{-1}	
Cytoplasmic State		
Viscosity	~ 0.01 Pa.s	~ 10 Pa.s
Structure	Liquid Passive	Liquid/Gel with Organelles Responds to Activation

that bulk viscosity is not usually elevated.[45] Although described as hyperviscosity syndromes, symptoms of leukaemia therefore probably arise in the microcirculation, induced by vascular obstruction at the cellular level. The circulatory problems are likely to be worse when poorly deformable blast cells are present.[46]

Blood/Vessel Wall Interactions

Adhesion of both red and white cells to vascular endothelium has been referred to above. Their contribution to ischaemia may not be simply obstructive. As pointed out, neutrophils can cause local tissue damage when activated. Adhesion of red cells to endothelium has also been suggested as a source of mechanical damage.[47] Damage to endothelium could cause platelet deposition. There is thus the possibility that flow-induced damage by adhesive or colliding blood cells could indirectly lead to thrombosis and vascular obstruction.

Relation Between Rheological Factors and Ischaemia

It is true that changes in the rheological properties of the blood can affect circulatory flow. The question remains: what degree of change is necessary to cause or contribute to ischaemic disease? When evaluating the role of rheological factors, one might consider the following questions:

—What is the magnitude of any abnormality or change in the disease group compared to the normal range of variation in rheological properties?

—Is the abnormality a cause or consequence of the disease?

—Could rheological factors predispose to ischaemia or accelerate other causative factors?

—Do other pre-existing conditions magnify the effect of rheological abnormalities—or indeed, lead quite normal rheological phenomena to excaberate flow reduction?

—Even if a rheological abnormality is a marker for disease rather than a causative factor, might it have prognostic or diagnostic value, or aid evaluation of treatment?

The normal range of values for some rheological properties is wide (e.g. blood viscosity). For others (e.g. red cell deformability), quite marked changes can be accommodated without ischaemic complications. Thus, only severe abnormalities are likely to be primary causes of ischaemia (e.g. in hyperviscosity syndromes, polycythaemia and sickle cell disease). On the other hand, rheological abnormalities may influence the progress of ischaemia. Here it is hard to separate a contributing factor from a coincidental change in rheology. Increases in plasma viscosity, red cell aggregation and whole blood viscosity may commonly occur in conjunction with an acute phase response. These changes may or may not significantly affect oxygen delivery. Another way in which rheological abnormalities could promote ischaemia is by pre-disposing to venous thrombosis.[48] Here, it has been suggested that increases in red cell aggregation and rigidity, haematocrit and fibrinogen all have the capability to promote thromosis.

The greatest potential for a secondary rheological contribution to ischaemia is in low flow states, where even normal rheological phenomena could excaberate the condition. Examples might be following a vaso-occlusive event, in venous insufficiency and in shock. Two suggestions are made in Figure 2:

(1) Reduction of flow rate leads to increasing red cell aggregation and increasing blood viscosity. These parameters may or may not have been within the normal range initially. Flow resistance and local vascular pressure then increases. Fluid loss may occur, with local haemoconcentration, elevation of haematocrit and plasma proteins. Further aggregation and viscosity rises follow, with increased resistance.

(2) Reduction of perfusion pressure may promote vascular obstruction by white cells. Trapped cells may become activated, causing vascular damage, release of stimulating factors and changes in the properties of newly arriving cells. This could result in further vascular occlusion and increased resistance. The above processes are not mutually exclusive and could lead to vicious cycles of increasing vascular resistance.

Blood Rheology and the Eye

Inferences regarding the role of rheological changes in ischaemia must be drawn from diverse clinical conditions. The eye, however, is a specialised organ with an atypical circulatory arrangement, particularly in its supply to the retina.[49] The arterial system is at a high pressure. The pressure in the veins is also elevated, because of the ambient intraocular pressure and a high venous flow resistance. Veins and arteries exist in close juxtaposition, and veins can become compressed at crossing points. Moreover, the metabolism and respiration of the retina are extremely high. The retinal circulation is thus considered to have a limited ability to adapt to rheological abnormalities, and may be particularly susceptible to rheological changes.[50]

Haemorheological aspects of ocular disease and ischaemia have recently been reviewed by Foulds.[51] Distinction is drawn between overtly abnormal haemorheology (hyperviscosity syndromes, polycythaemia, leukaemia, sickle cell disease), and a range of conditions where evidence of abnormal blood rheology exists, but where the role in ocular disease is uncertain (ischaemic optic neuropathy, venous insufficiency retinopathy, hyperlipidaemia, diabetes, open angle glaucoma). Lowe[48] has pointed out that 'after the veins of the lower limb and pelvis, spontaneous venous occlusion occurs most commonly in the retinal vein', and suggests that rheological as well as vascular factors may be involved. In the context of retinal vein occlusion, Shilling notes

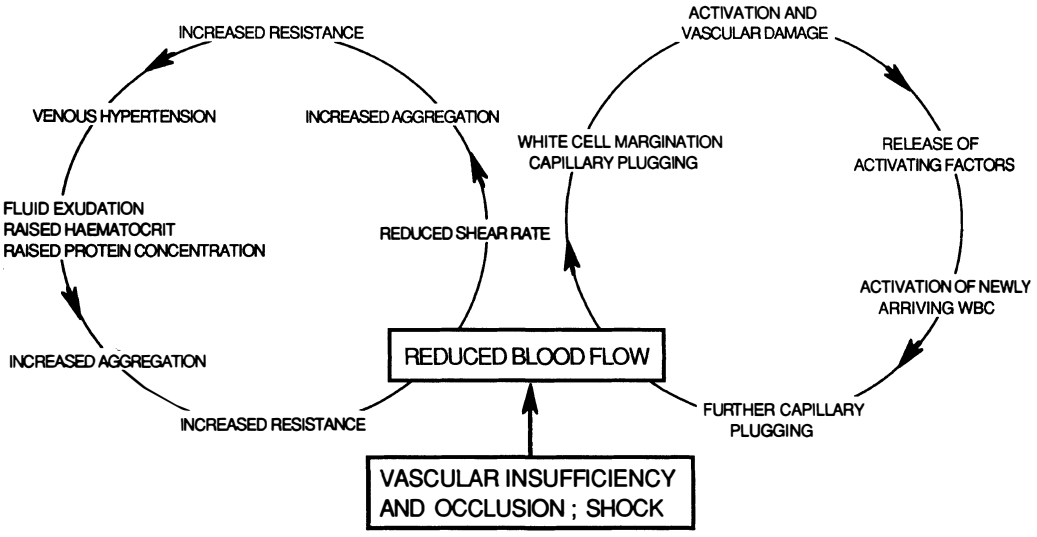

Fig. 1. *Cycles of rheological changes initiated by flow reduction (adapted from Nash & Dormandy[2]).*

that investigations of blood viscosity have been disappointing in trying to understand the cause of occlusion on a patient-by-patient basis.[52] In deciding an aetiological role for rheological factors, perhaps the acid test is whether rheological treatment improves the clinical state of the patient. Plasmapherisis, leukapherisis and venesection have accepted therapeutic roles in hyperviscosity syndromes, leukaemia and polycythaemia,[4,44,51] but definitive studies remain to be done in other putative rheological syndromes.

Keywords: Blood Rheology, Circulation, Erythrocyte, Eye, Ischaemia, Leukocyte.

References

[1] Chien S: Physiological and pathophysiological significance of hemorheology. In Chien S, Dormandy J, Ernst E, Matrai A, eds. Clinical haemorheology. Dordrecht: Martinus Nijhoff 1987: 125–164.

[2] Nash GB and Dormandy JA: The involvement of red cell aggregation and blood cell rigidity in impaired microcirculatory efficiency and oxygen delivery. In Fleming JS, ed. Drugs and the delivery of oxygen to tissue. Boca Raton: CRC Press, 1990; 227–252.

[3] Laurence JH: Polcythaemia. New York: Grune and Stratton, 1955.

[4] Luxenberg MN: Hematologic and reticuloendothelial diseases and their relation to the eye. In Mausolf FA, ed. The eye and systemic disease. St. Louis: C.V. Mosby, 1980: 305–324.

[5] Holt JM and Gordon-Smith EC: Retinal abnormalities in diseases of the blood. *Br J Ophthalmol* 1969, **203:** 145–60.

[6] Harkness J: The viscosity of human blood plasma; its measurement in health and disease. *Biorheology* 1971, **8:** 171–93

[7] McGrath MA and Penny R: Paraproteinaemia: Blood hyperviscosity and clinical manifestations. *J Clin Invest* 1976, **58:** 1155–62.

[8] Somer T: Rheology of paraproteinaemias and the plasma hyperviscosity syndrome. *Balliere's Clinical Haematology* 1987, **3:** 695–723.

[9] Volger E, Schmid-Schonbein H, v Gosen J, Klose HJ, Kline KA: Microrheology and light transmission of blood. *Pflugers Arch* 1975, **354:** 319–37.

[10] Janzen J and Brooks DE: Do plasma proteins absorb to red cells? *Clinical Haemorheology* 1989, **9:** 695–714.

[11] Chien S, Usami S, Dellenback RJ, Gregersen MI: Shear dependent interaction of plasma proteins with erythrocytes in blood rheology. *Am J Physiol* 1970, **219:** 143–53.

[12] Lipowsky HH, Kovalchek S, Zweifach BW: The distribution of blood rheological parameters in the microcirculation of cat mesentery. *Circ Res* 1978, **43:** 738–49.

[13] Sigel B, Machi J, Beitler JC, Justin JR, Coelho JC: Variable ultrasound echogenicity in flowing blood. *Science* 1982, **218:** 1321–3.

[14] Kiesewetter H: The yield shear stress of blood in branched models of the microcirculation: Effect of haematocrit and plasma macro-molecules. *Bibl Haematol* 1981, **47:** 14–20.

[15] Reinke W, Johnson PC, Gaehtgens P: Effect of shear rate on apparent viscosity of human blood in tubes of 29 to 94 μm diameter. *Circ Res* 1986, **59:** 124–32.

[16] Trope GE, Lowe GDO, McArdle BW, Douglas JT, Forbes CD, Prentice CRM, Foulds WS: Abnormal blood viscosity and haemostasis in long-standing retinal vein occlusion. *Br J Ophthalmol* 1983, **67:** 137–42.

[17] Chabanel A, Glacet-Bernard A, Lelong F, Taccoen A, Coscas G, Samama MM: Increased red blood cell aggregation in retinal vein occlusion. *Br J Haematol* 1990, **75:** 127–31.

[18] Nash GB, Johnson CS, Meiselman HJ: Mechanical properties of oxygenated red blood cells in sickle cell (HbSS) disease. *Blood* 1984, 73–82.

[19] Chien S, King RG, Kaperonis AA, Usami S: Viscoelastic properties of sickle cells and hemoglobin. *Blood Cells* 1982, **8:** 53–65.

[20] Nash GB, Johnson CS, Meiselman HJ: Influence of oxygen tension on the viscoelastic behaviour of red blood cells in sickle cell disease. *Blood* 1986, **67:** 110–8.

[21] Stuart J and Nash GB: Red cell deformability and haematological disorders. *Blood Reviews* 1990, **4:** 141–7.

[22] Brain MC: Hematologic and reticuloendothelial diseases. In Mausolf FA, ed. The eye and systemic disease. St. Louis: C. V. Mosby, 1980; 294–304.

[23] Saul A, Lamont G, Sawyer WH, Kidson C: Decreased membrane deformability in melanesian ovalocytes from Papua New Guinea. *J Cell Biol* 1984, **98:** 1348–54.

[24] Stuart J and Juhan-Vague I: Erythrocyte rheology in diabetes mellitus. *Clinical Haemorheology* 1987, **7:** 239–45.

[25] Kaul DK, Fabry ME, Nagel RL: Microvascular sites and characteristics of sickle cell adhesion to vascular endothelium in shear flow conditions. *Proc Nat Acad Sci* (USA) 1989, **86:** 3356–60.

[26] Luse SA and Miller LH: Plasmodium falciparum malaria: Ultrastructures of parasitized erythrocytes in cardiac vessels. *Am J Trop Med Hyg* 1971, **20:** 655–60.

[27] Howard RJ and Gilladoga AD: Molecular studies related to the pathogenesis of cerebral malaria. *Blood* 1989, **74:** 2603–18.

[28] Hebbel RB, Moldow CF, Steinberg MH: Modulation of erythrocyte-endothelial interactions and the vasocclusive severity of sickling disorders. *Blood* 1981, **58:** 947–52.

[29] Mohandas N and Evans EA: Adherence of sickle erythrocytes to vascular endothelial cells: Requirement for both cell membrane changes and plasma factors. *Blood* 1984, **64:** 282–7.

[30] Wautier JL, Paton RC, Wautier MP, Pintigny D, Abadie E, Passa P, Caen JP: Increased adhesion of erythrocytes to endothelial cells in diabetes

mellitus and its relation to vascular complications. *New Eng J Med* 1981, **305:** 237–42.

[31] Smith BD, Thomas JL, Gillespie JA: Abnormal erythrocyte endothelial adherence in ischemic heart disease. *Clinical Haemorheology* 1990, **10:** 241–53.

[32] Kovacs IB, Rustin MH, Thomas RH, Ridler C, Sowemimo-Coker SO, Kirby JD: Plasma or serum from patients with systemic sclerosis alters behaviour of normal erythrocytes. *Ann Rheum Dis* 1985, **44:** 395–8.

[33] Schmid-Schonbein GW, Shih YY, Chien S: Morphometry of human leukocytes. *Blood* 1980, **56:** 866–75.

[34] Chien S, Schmid-Schonbein GW, Sung KLP, Schmalzer EA, Skalak R: Viscoleastic properties of leukocytes. In Meiselman HJ, Lichtman MA, LaCelle PL, eds. White cell mechanics: basic science and clinical aspects. New York: Alan R. Liss 1984: 19–51.

[35] Nash GB and Meiselman HJ: Rheological properties of individual polymorphonuclear granulocytes and lymphocytes. *Clinical Haemorheology* 1986, **6:** 87–97.

[36] Brooks DE and Evans EA: Rheology of blood cells. In Chien S, Dormandy J, Ernst E, Matrai A, eds. Clinical haemorheology. Dordrecht: Martinus Nijhoff 1987: 73–96.

[37] Bagge U and Branemark P-I: White blood cell rheology. An intravital study in man. *Adv Microcirc* 1977, **7:** 1–17.

[38] Bagge U: Leukocytes and capillary perfusion in shock. In Meiselman HJ, Lichtman MA, LaCelle PL, eds. White cell mechanics: basic science and clinical aspects. New York: Alan R. Liss 1984: 285–94.

[39] Engler RL, Schmid-Schonbein GW, Pavelec RS: Leukocyte plugging in myocardial ischaemia and reperfusion in the dog. *Am J Pathol* 1983, **111:** 98–111.

[40] Nash GB, Jones JG, Mikita J, Christopher B, Dormandy JA: Effects of preparative procedures and of cell activation on flow of white cells through micropore filters. *Br J Haematol* 1988, **70:** 171–6.

[41] Harlan JM: Leukocyte-endothelial interactions. *Blood* 1985, **65:** 513–25.

[42] Schmid-Schonbein GW: Mechanisms of granulocyte-capillary-plugging. *Prog Appl Microcirc* 1987, **12:** 223–30.

[43] Lucchesi BR and Mulľane KM: Leukocytes and ischaemia-induced myocardial injury. *Ann Rev Pharmacol* 1986, **26:** 201–24.

[44] Mehta B, Goldman JM, Kohner EM: Hyperleukocytic retinopathy in chronic granulocytic leukaemia: The role of intensive leukapherisis. *Br J Haematol* 1984, **56:** 661–7.

[45] Lichtman MA and Rowe JM: Hyperleukocytic leukemias: Rheological, clinical and therapeutic considerations. *Blood* 1982, **60:** 179–83.

[46] Lichtman MA: Rheology of leukocytes, leukocyte suspensions and blood in leukemia: possible relationship to clinical manifestations. *J Clin Invest* 1973, **52:** 350–8.

[47] Wautier JL, Pintigny D, Maclouf J, Wautier MP, Corvazier E, Caen JP: Release of prostacyclin after erythrocyte adhesion to cultured vascular endothelium. *J Lab Clin Med* 1986, **107:** 210–5.

[48] Lowe GDO: Blood rheology and venous thrombosis. *Clinical Haemorheology* 1984, **4:** 571–88.

[49] Trevor-Roper PD and Curran PV: The eye and its disorders. 2nd ed. Oxford: Blackwell. 1984: 43.

[50] McGrath MA, Wechsler F, Hunyor ABL, Penny R: Systemic factors contributing to retinal vein occlusion. *Arch Intern Med* 1978, **138:** 216–20.

[51] Foulds WS: 'Blood is thicker than water' Some haemorheological aspects of ocular disease. *Eye* 1987, **1:** 343–63.

[52] Shilling JS: Retinal vein occlusion. In Kanski JJ, Morse PH, eds. Disorders of the vitreous, retina and choroid. London: Butterworths 1983: 115–121.