Eye (1987) **1**, 343–363

50th BOWMAN LECTURE

'Blood is Thicker Than Water' Some Haemorheological Aspects of Ocular Disease

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Just under 100 years ago the first Bowman Lecture on 'The Relation of Certain Diseases of the Eye to Gout' was presented at the Society's Annual Congress by Jonathan Hutchinson.[1] It goes without saying that I am deeply honoured to have been asked to present the 50th Anniversary Lecture in commemoration of Sir William Bowman. By an odd coincidence, just 50 years ago to the day, the building which at present houses the Tennent Institute of Ophthalmology in Glasgow was opened so simultaneously I am celebrating two fiftieth anniversaries.

Bowman as everyone knows was the first President of the OSUK and the most famous ophthalmologist of his day. His contributions ranged from anatomy and physiology to surgery, and he was one of the first in the United Kingdom to use the operation for glaucoma introduced by von Graefe with whom he was recorded for posterity in a fine photograph (Fig. 1).

Bowman lived and worked in an age where advanced pathology was common and the available remedies few and of doubtful efficacy. Colour photographs taken in the Tennent Institute at the beginning of this century give an indication of the clinical problems Bowman had to face (Figs 2, 3). How would today's ophthalmologist like to treat advanced sepsis without the benefits of antibiotics or buphthalmos without the benefits of anaesthesia?

One of a series of lectures given by Bowman to the Royal London Ophthalmic Hospital in 1848 was entitled 'A Case of Cataract Extraction—Sight Remaining' which says something about cataract surgery at that time. In the same book of lectures a woman with bilateral acute glaucoma is described. The poor woman's eyes apparently ruptured but Bowman with true scientific detachment praised

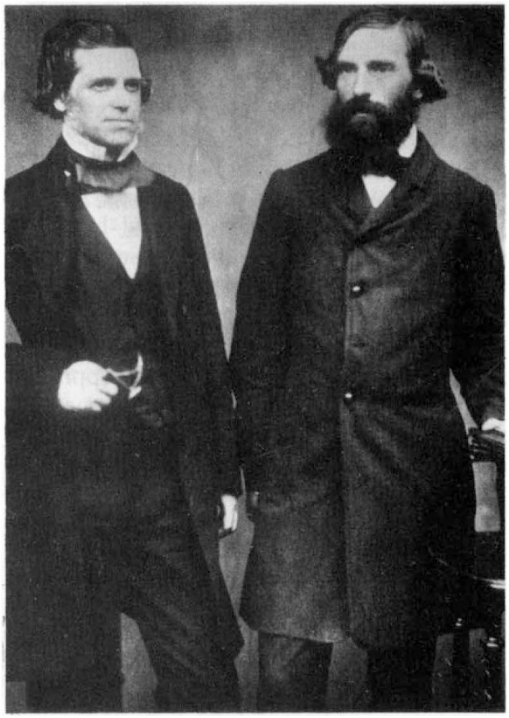

Fig. 1. *William Bowman and Albrecht v Graefe photographed together.*

Presented at the Annual Congress of the Ophthalmological Society of the United Kingdom, April 1986.

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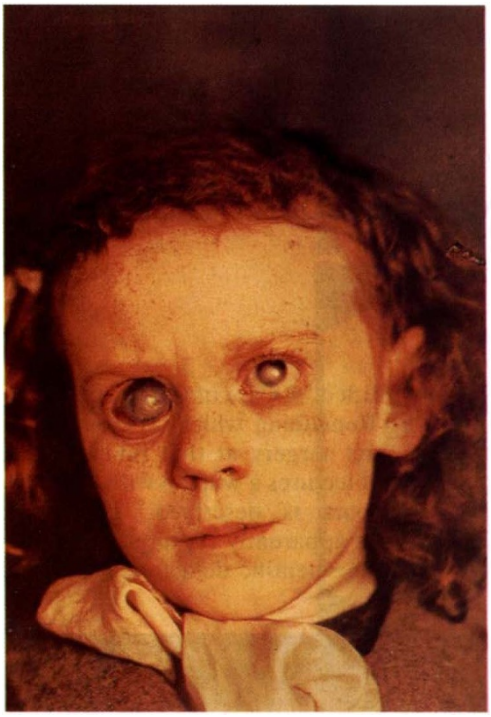

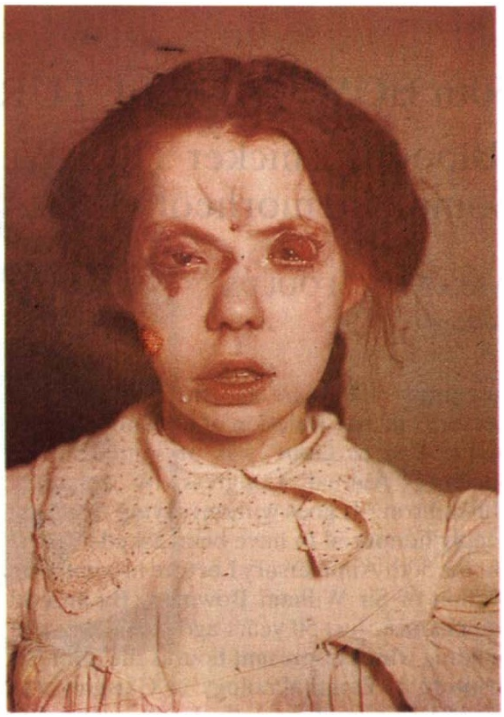

Figs 2 and 3. *Colour photographs taken in 1910 in the Tennent Institute to illustrate the advanced pathology which was common before the advent of antibiotics and other currently available therapies.*

the House Surgeon for retrieving the retinae intact for histological examination.[2]

When the establishment of a Bowman Lecture was proposed in 1883 at the suggestion of Dr. Gowers, the famous physician, it was intended that the Lecture should be a critical summary upon some special subject approved by the Council. Bowman was a generalist rather than a specialist and the subject I have chosen for my lecture concerns one aspect of the many inter-relationships there are between the health of the body and that of the eye.

I have chosen as a title the phrase 'blood is thicker than water' and although you may have thought that I was going to talk about genetics I am actually going to concentrate on the blood itself and particularly its physical attributes in relation to ocular disease.

Physical Characteristics of Blood in relation to Blood Flow

We are all aware of the importance of the blood vascular system in many eye disorders but we tend to think more often of the vessels themselves than we do of the quality of the circulating blood, even although when we look at the ocular fundus with an ophthalmoscope it is the blood in the vessels we see and not the vessels themselves.

In addition to its hydrostatic pressure the physical properties of the blood include its colloid osmotic pressure and its viscosity the latter determined both by the molecular and the cellular components of this complex fluid.

When blood flows through vessels such as the retinal vessels its flow resistance is related both to the cross-sectional area of the vessel in which it is flowing and to its viscosity. The factors which contribute to the resistance to the flow of fluids were quantified by Hagen and by Poiseuille for laminar flow in straight tubes. The well-known Hagen-Poiseuille law relates flow rate to the pressure gradient, the radius of the tube to the fourth power and inversely to the length of the tube and the viscosity. In practice blood flow is much more complex than this because vessels are neither

single tubes nor straight, and blood itself has complex rheological characteristics which relate to the macro-molecules of the plasma and the presence of cellular elements in this complex fluid.

Where flow is non-turbulent it has a laminar character, well seen in fluorescein angiograms in the venous phase (Fig. 4). The flow rate varies considerably across the width of the vessel being slowest next to the wall where frictional resistance is high and fastest axially where the cellular elements of the blood are concentrated. Between the axial column of blood in the centre of the blood vessel and the walls of the vessel one can imagine a series of layers of plasma each sliding one upon the other. Blood viscosity can be thought of as resistance to this sliding.

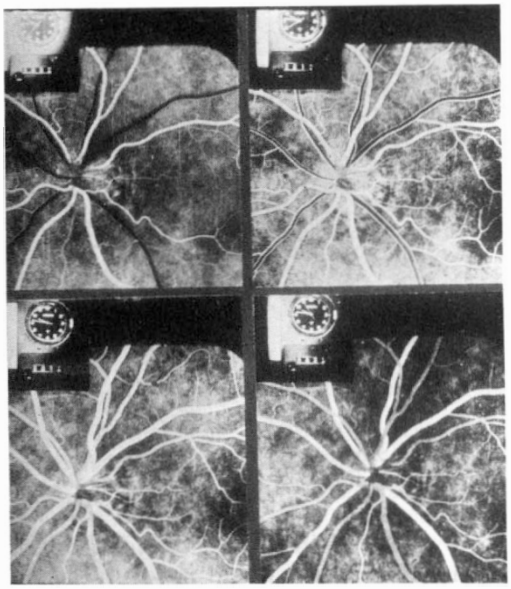

Fig. 4. *Normal fluorescein angiogram. Laminar flow is evident in the venous phase.*

Plasma Viscosity

Plasma itself behaves like a simple homogeneous fluid and its viscosity can be measured by timing its passage through a capillary tube under a given head of pressure at a constant temperature (Fig. 5). Normal plasma at 37 °C is about one-and-a-half times as viscous as water (1.4–1.6 in our laboratory).

The many large molecules present in the plasma contribute to its physical characteristics and important among these are the plasma proteins. With their larger molecular weights and irregular shape the globulins contribute more to viscosity than the lower molecular weight albumins although the latter may make up in quantity what they lack in molecular size. Clinically the immunoglobulins and the fibrinogen of the plasma appear to be the most important factors in relation to retinal vascular disorders associated with increased plasma viscosity. The fibrinogen molecule is not only large (MW 350,000) but very asymmetrical and so contributes much more to plasma viscosity than its relatively low concentration in plasma might suggest.

Another constituent of the blood with an important physical role is the lipid which is present mainly as lipoprotein or as glycolipid. There is a correlation between triglyceride levels and plasma viscosity mainly because of the increased amounts of very low density lipoprotein present in hypertriglyceridaemia.[3] This lipoprotein has a molecular weight of some 3,000,000 and is therefore rheologically important.

The effective viscosity of blood flowing in a blood vessel is not independent of the rate of flow. A fluid such as blood which contains cells and large irregular protein molecules changes its effective viscosity with the shear rate, i.e. the rate at which separate layers of the bloodstream can be thought of as sliding one upon the other. To a degree the shear rate can be equated with flow rate. Because whole blood viscosity varies with shear rate its measurement has to be made with an instrument which allows one to determine the effective viscosity at different rates of shear. We have used a cone viscometer (Contraves) where the drag exerted by a blood sample on a cone dipped into the sample and rotating at a variety of speeds allows us to measure whole blood viscosity at different shear rates. At high shear rates (100 s^{-1}) whole blood is about seven times as viscous as water, while at low shear rates (0.1 s^{-1}) it may be one hundred times as viscous. The contribution to flow resistance offered by whole blood viscosity is therefore much greater where blood flow is slow as in the veins than where it is fast as in the arteries. In the eye therefore the most

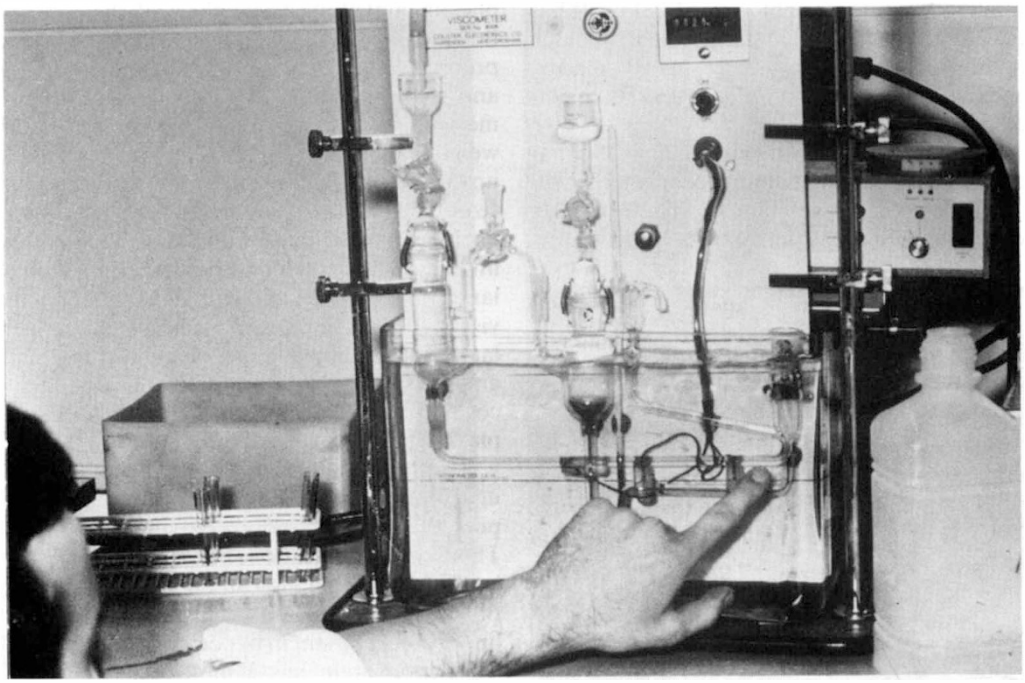

Fig. 5. *A simple capillary viscometer used for the measurement of plasma viscosity. The plasma is driven along a capillary tube in a water bath by a head of pressure and the rate of movement of the leading meniscus is timed electronically.*

obvious manifestation of increased blood viscosity is retinal venous dilatation.

Red and White Cell Deformability

In addition to plasma viscosity and whole blood viscosity an important rheological factor is the deformability of the red cells and the white cells. Red cells have of course to deform considerably to pass through capillaries many of which are of a smaller diameter than the red cell (Fig. 6).

To some extent the deformability of a red cell depends on its shape and the question of why red cells are the shape they are is a fascinating one which was addressed by Lehmann, well known for his work on the haemoglobinopathies.[4] Haemoglobin, as we all know, is a most efficient carrier of oxygen and indeed mammalian blood can carry fifty times more oxygen than saline. There is some advantage in having haemoglobin in cells rather than in the plasma. If our haemoglobin were in the plasma it is estimated that either we would require four times as much haemoglobin which would make the blood unacceptably viscous, or would require a blood volume of some twenty litres rather than five which might make us fairly immobile! Alternatively we would need a cardiac output four times as great which could be difficult to achieve.

In nearly all species with red cells the thickness of the cells *in vitro* is around 2 μ which is that best suited to the penetration of oxygen to combine with the contained haemoglobin. The diameters of red cells seem to relate to the dimension of the capillaries through which they have to pass although in man many of these capillaries are of a narrower bore than the average red cell diameter of close on 8 μ. The bi-concave shape of the red cell not only allows a uniform distribution of oxygen in the cell, but by increasing the surface area to the volume aids gaseous exchange and allows alterations in cell volume and shape without stressing the cell membrane. Each red cell contains 400,000,000 molecules of

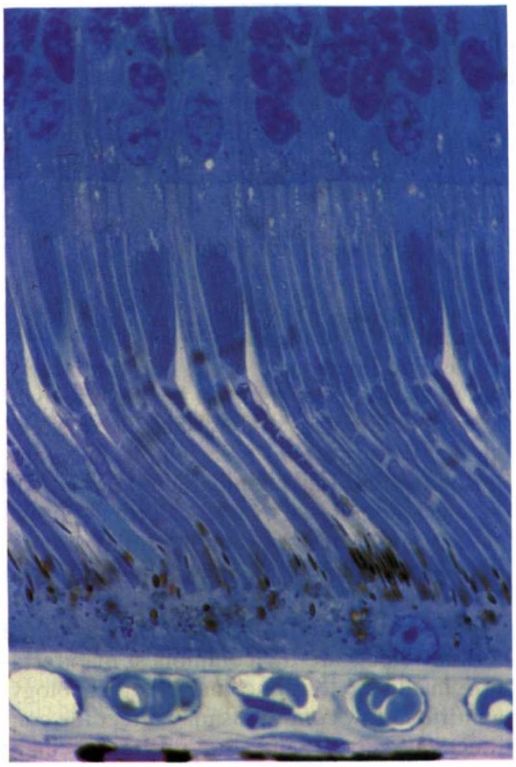

Fig. 6. *Light micrograph of the retina and choroid. Red cells in the choriocapillaris are moderately deformed as they pass through the capillary bed. (×1,500)*

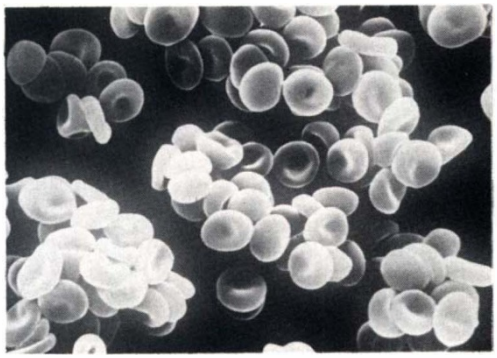

Fig. 7. *Scanning electromicrograph of red cells* in vitro *demonstrating their conventional biconcave shape. (×2,500)*

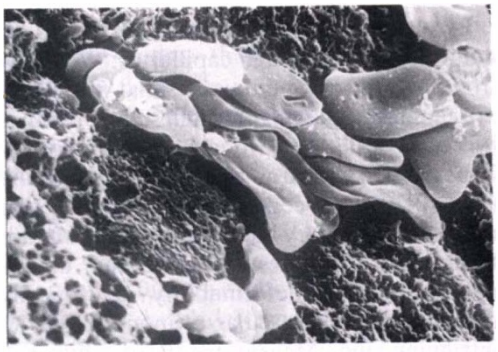

Fig. 8a

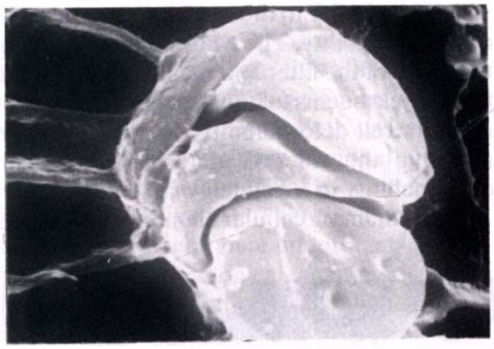

Fig. 8a, b. *Scanning electronmicrographs of red cells in retinal capillaries showing extreme deformation of the cells as they pass through the capillaries. ((a) ×6,000, (b) ×11,500)*

haemoglobin all packed together with maximum efficiency and supported by structural proteins which together give the cell a certain rigidity. *In vivo* many of the red cells lose their bi-concave shape and become streamlined to reduce viscosity and aid their passage through capillaries(Figs 7, 8). This ability to deform is vital to unimpeded capillary blood flow and is greatly aided by the ability of the red cell membrane to rotate around the cytoplasm. At capillary level simple considerations of whole blood viscosity in relation to flow cease to be applicable and factors such as red cell or white cell deformability become much more important.

Measurement of red cell deformability *in vitro* is difficult as it is impossible to reproduce exactly the *in vivo* situation. One way is to measure the resistance to the passage of red cells through a filter with a pore size less than the average red cell diameter. Commonly a pore size of 5 μ is used (Fig. 9). The technique has now been computerized and results are highly reproducible. Measurements of red cell filterability give results of some interest in a number of different eye disorders.

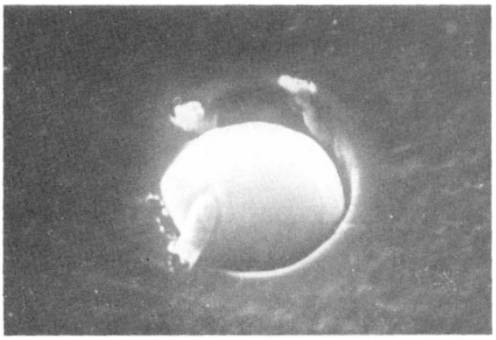

Fig. 9. *Scanning electronmicrograph of the surface of the filter used to measure red cell filterability. A red cell is seen passing through one of the pores which measure 5 μ in diameter. (×12,000)*

Like red cells, white cells also need to deform to pass through capillaries. We know from their behaviour in tissues that white cells are capable of passing through small openings in vessel walls or through such apparently impervious structures as Bruch's membrane (Fig. 10). The process is, however, slow and in relation to capillary blood flow white cells are fairly rigid. The question of whether abnormal white cell deformability is clinically important in the vascular retinopathies is an intriguing one. Measurements of white cell deformability can be made using techniques which are similar to those used to measure red cell deformability. The white cells tend to clog the pores of the filter and the rate at which the filter blocks seems to be a useful measurement of white cell deformability. Currently we are assessing the role of abnormal white cell deformability in a number of eye disorders.[5]

The remaining cellular element in the blood is, of course, the platelets. Their small size makes it unlikely that they are of rheological importance but their role in relation to thrombosis is well known. The complex relationship of platelets, prostaglandins, lipid metabolism, thrombus inducing and thrombus inhibiting factors is an area of great interest at present in relation to many cardiovascular disorders including diabetic retinopathy.

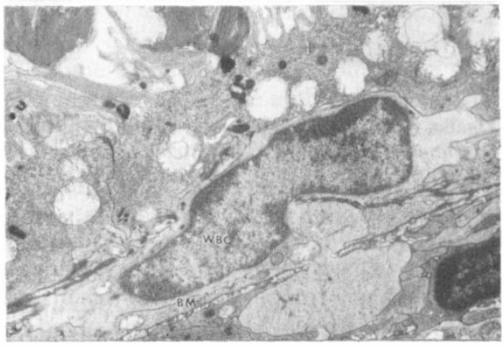

Fig. 10. *Light micrograph to show a white cell (WBC) passing through Bruch's membrane (BM). (×6,000)*

Abnormal Blood Rheology

Having outlined some of the determinants of blood rheology let us consider the effects of abnormal rheology. Abnormal blood rheology may be overt in, for example, the paraproteinaemias, the haemoglobinopathies and in the leukaemias. Covert effects of abnormal rheology may be important in retinal vascular occlusions, diabetic retinopathy and even glaucoma.

While it is true that visible changes in the retinal vessels are the commonest manifestation in the eye of abnormal blood rheology, abnormal flow conditions may affect the conjunctival vessels and the posterior ciliary vessels.

The retina with its high metabolic rate is very sensitive to alterations in blood supply and the need to maintain a high intraluminal pressure in both the retinal arteries and veins to counteract the intraocular pressure brings its own problems. It has been suggested that the anatomical arrangements required to maintain high flow resistance in the central retinal vein at the optic nerve head may limit the ability of the retinal circulation to adapt to increased blood viscosity[6] and indeed the eye has been likened to a clinical viscometer.[7]

Abnormalities of Red Cell Shape

The rheological properties of the blood may be altered either by a change in the constituents of the plasma or of the cellular elements of the blood. As already indicated the ability of the red cells to deform is important in relation to capillary blood flow. As the shape of the red cell is probably largely dependent on the shape and packing of the haemoglobin molecules and other proteins present, any change in the haemoglobin molecules could

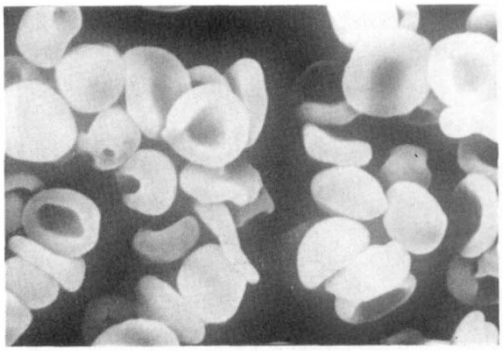

Fig. 11a

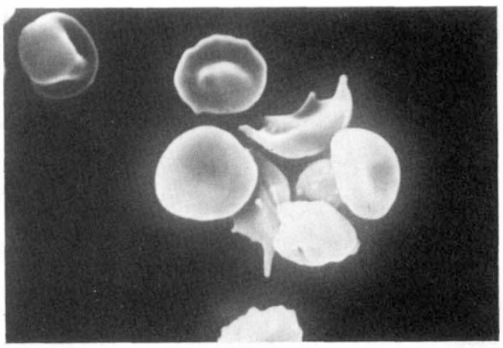

Fig. 11b

Fig. 11. *Scanning electronmicrograph of red blood cells in sickle cell anaemia, (a) unsickled, (b) demonstrating sickling when the haemoglobin is reduced. ((a) ×5,000, (b) ×5,000)*

have a marked effect on both the shape and the deformability of the red cell.

In the sickle cell disorders abnormally shaped red cells are associated with occlusive retinal vascular disease and when one sees the extremely abnormal shape of sickled cells (Fig. 11) it is no surprise that microvascular occlusions occur in this condition. The abnormal shape of the haemoglobin molecule in the sickling disorders is associated with the reduced form of haemoglobin and therefore with hypoxia. In the eye the peripheral retina is less well supplied with oxygen than is the central retina and so sickling tends to be more marked in the peripheral retina and it is in the peripheral retina that vascular occlusions occur (Fig. 12).[8,9,10]

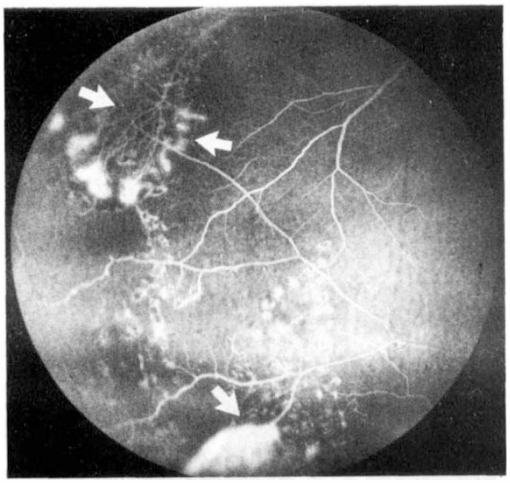

Fig. 12. *Fluorescein angiogram of typical 'seafans' (arrowed) of retinal neovascularisation in sickle cell disease. The abnormal deformability of sickled red cells leads to vascular closure and neovascularisation. The discrete hyperfluorescent lesions are laser burns.*

Another example of a disorder in which the red cells are grossly abnormal in shape is the Bassen Kornzweig syndrome[11] where the red cells have spines giving them the name acanthocytes (Fig. 13). These abnormally shaped red cells are fragile and haemolytic anaemia is a feature of this disorder. We have measured red cell deformability in one case and found it to be greatly reduced. One might well imagine that retinal vascular occlusions would be common in this disease but this appears not to be the case, and certainly in two cases under my care there has been no evidence of this complication in spite of extreme acanthocytosis in both cases and a well developed pigmentary retinopathy which is, of course, the main ocular characteristic of this disorder (Fig. 14). There is a possibility that the concurrent anaemia protects against the abnormal rheological characteristics of the red cells in abetalipoproteinaemia.

The blood in patients with pernicious anaemia is characterised by marked anisocytosis and macrocytosis (Fig. 15). It is easy to imagine that macrocytes might have difficulty in negotiating the smaller retinal capillaries (Fig. 16) and it seems a possibility that it is the presence of macrocytes in this type of anaemia which may give rise to the well known Roth spots[12] which characterise the retinopathy of pernicious anaemia. Histologically as Ashton in his Bowman Lecture has shown,[13] these spots show the typical features of nerve fibre

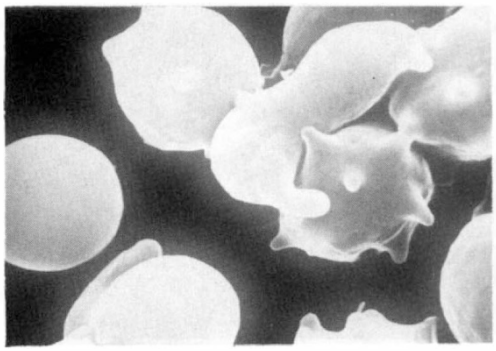

Fig. 13a

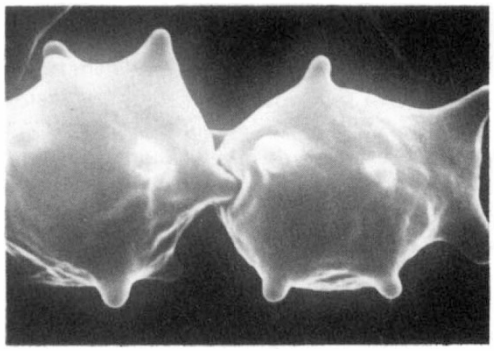

Fig. 13b

Fig. 13a, b. *Scanning electronmicrographs of red cells (acanthocytes) from patients with abetalipoproteinaemia. The grossly abnormal shape of the red cells is apparent. ((a) ×7,500, (b) ×11,000)*

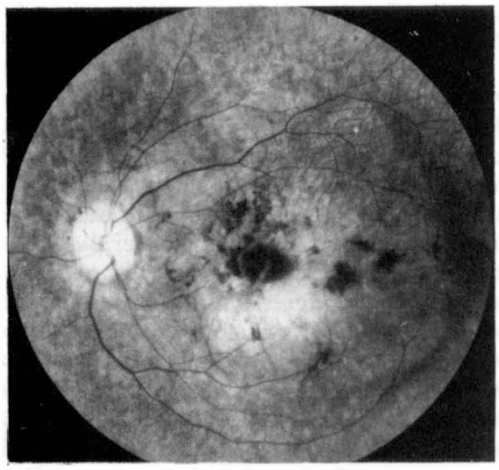

Fig. 14a

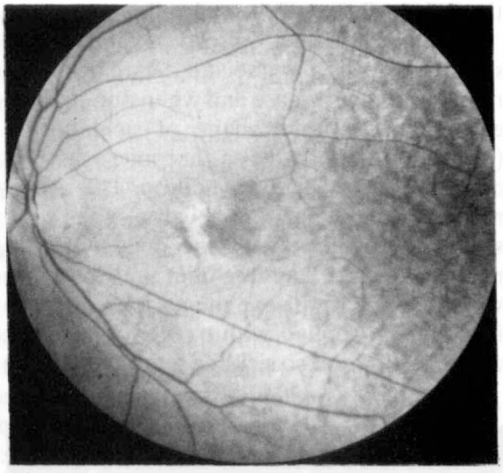

Fig. 14b

Fig. 14a, b. *Examples of pigmentary retinopathy in two cases of abetalipoproteinaemia.*

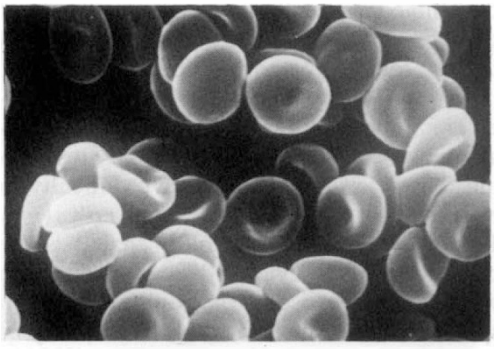

Fig. 15a

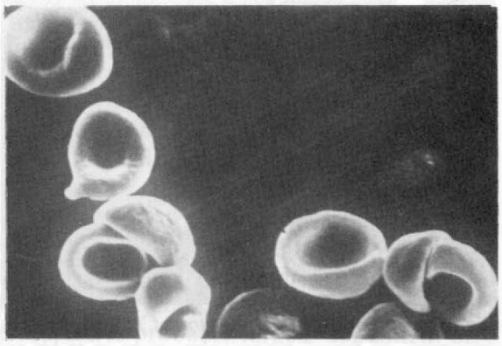

Fig. 15b

Fig. 15. *Scanning electronmicrograph of (a) normal red cells and (b) macrocytes in pernicious anaemia. ((a) ×5,000, (b) ×5,000)*

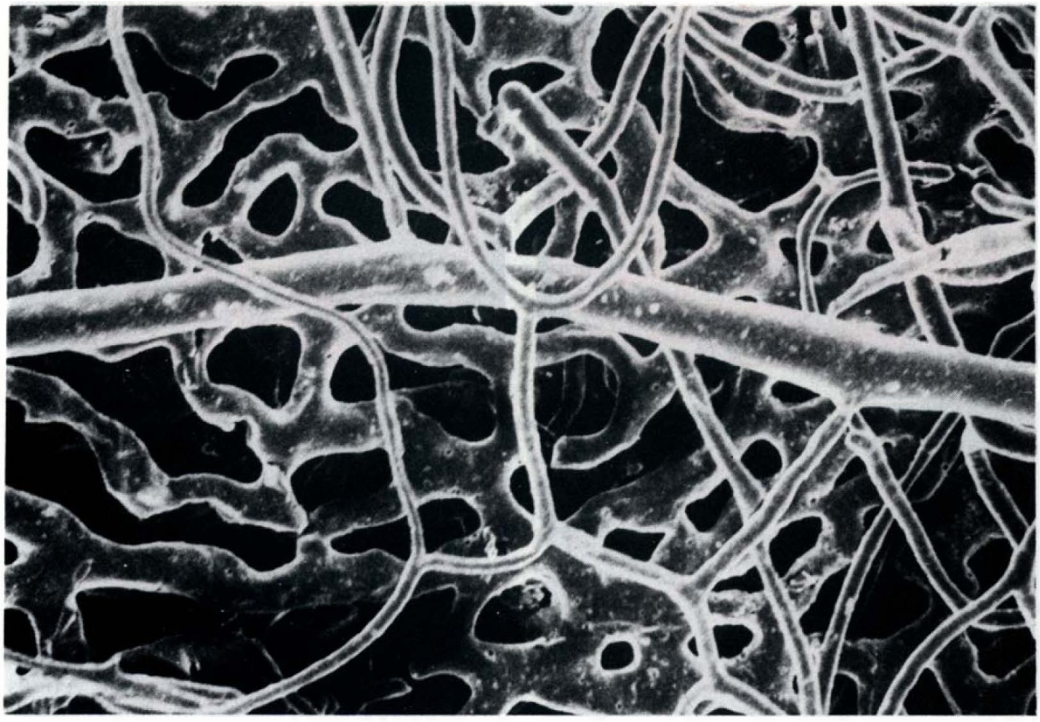

Fig. 16. *Scanning electronmicrograph of resin cast of human retinal and choroidal vessels. The retinal capillaries are much narrower than the underlying capillaries of choriocapillaris. (×500)*

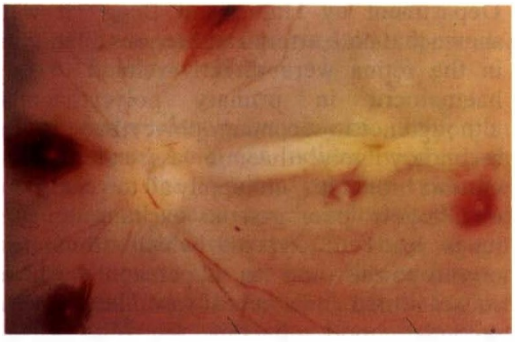

Fig. 17a

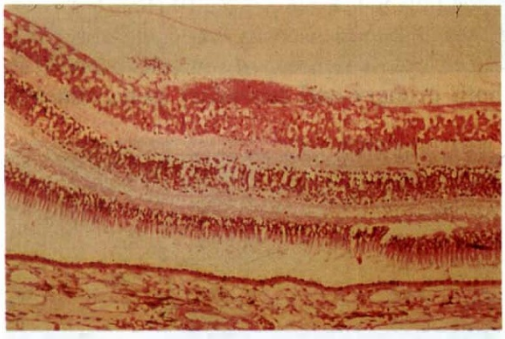

Fig. 17b

Fig. 17. *Macroscopic appearance (a) and microscopic appearance (b) of a Roth spot.*

layer infarcts with cytoid bodies and varicose nerve fibres indicating a blockage of axoplasmic transport and accounting for their white centres (Fig. 17). Why the infarcts in pernicious anaemia are haemorrhagic has to be explained and the explanation may be that the interruption to blood flow is only transient and that leakage of blood through damaged capillaries results when flow is re-established.*

These haemorrhagic infarcts with their white centres are much commoner in pernicious anaemia (Fig. 18) than in other types

*I am grateful to Professor W. R. Lee for this suggestion.

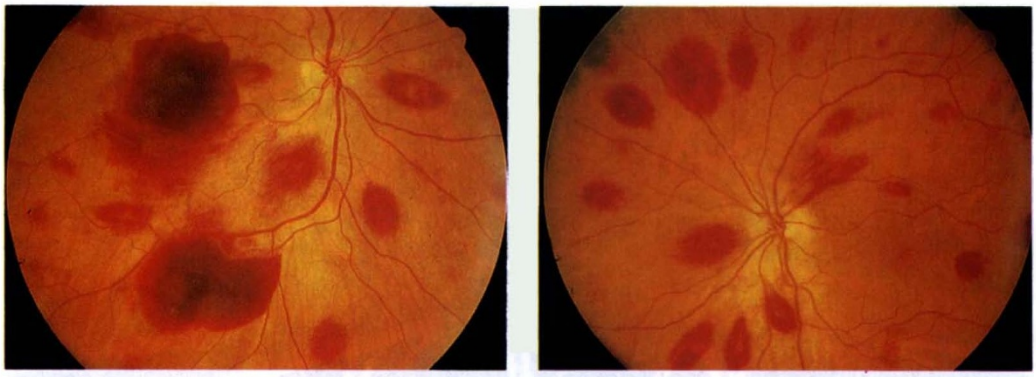

Fig. 18a Fig. 18b

Fig. 18. *The characteristic retinopathy of pernicious anaemia to show numerous Roth spots. (a) right eye, (b) left eye.*

of anaemia where the red cells are of normal dimensions or even microcytic. It would not be difficult to imagine temporary blockage of capillary flow in pernicious anaemia associated with the passage of very large macrocytes.

Anaemia and Polycythaemia

We need no reminding that the red cells carry oxygen and that anaemia can manifest itself as a haemorrhagic retinopathy particularly if the number of cells is reduced or the haemoglobin level falls below 6 g per cent[14] (Fig. 19).

Whole blood viscosity is considerably influenced by the number of red cells present. In both primary and secondary polycythaemia whole blood viscosity is raised particularly when measured at low shear rates. Indeed, it is possible to relate whole blood viscosity in such patients to the haematocrit, the critical level above which clinical signs related to hyperviscosity begin to be manifest being a PCV of 50.[15] In the eye, the raised viscosity in polycythaemia shows itself as retinal venous dilatation or even papilloedema and in passive congestion of the venous capillaries of the conjunctiva (Fig. 20).

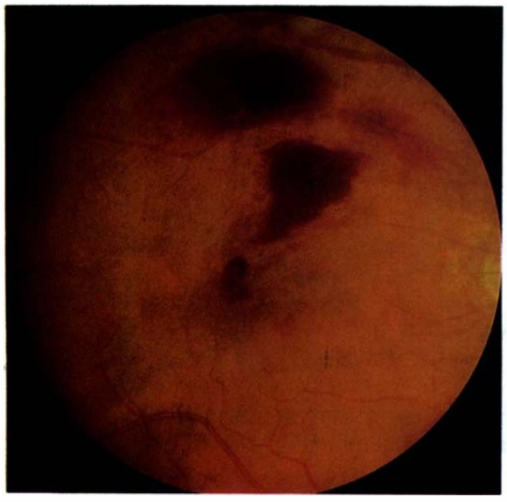

Fig. 19. *Haemorrhagic retinopathy in severe anaemia.*

In a study carried out many years ago in my Department by Hume and Begg[16] it was shown that both arterial and venous dilatation in the retina were directly related to the haematocrit in primary polycythaemia although not in secondary polycythaemia. In secondary polycythaemia associated with chronic bronchitis, unhappily all too common in Glasgow, poor gaseous exchange in the lungs leads to hypoxia which stimulates erythropoiesis and to hypercapnia which causes retinal and cerebral vasodilatation. In secondary polycythaemia the high PCO_2 levels tend to obscure any direct effect that increased blood viscosity may have on the retinal blood vasculature.

In the retinal veins of patients with polycythaemia the raised whole blood viscosity may result in a slowing of blood flow which in turn increases the effective viscosity leading to further slowing and eventually stagnation and venous thrombosis. In polycythaemia the incidence of myocardial infarction and of cerebral infarction can also be correlated with the haematocrit.[17] Interestingly, although a

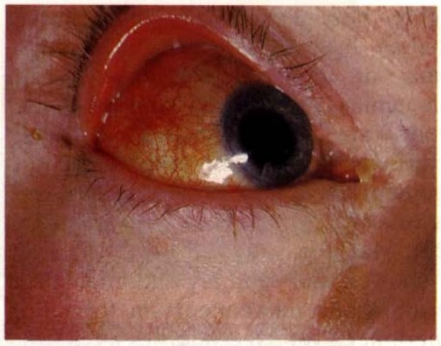

Fig. 20a

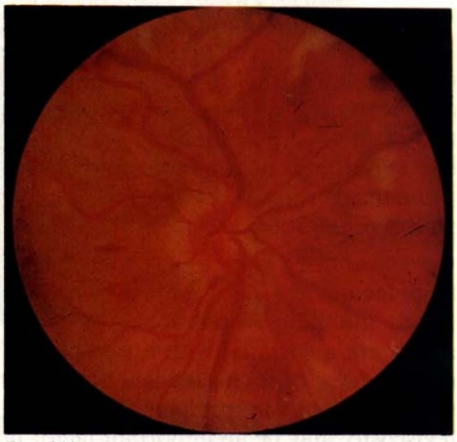

Fig. 20b

Fig. 20. *Polycythaemia. (a) conjunctival appearance and (b) appearance of fundus.*

marked secondary polycythaemia is common among South American Indians living at high altitude in the Andes, vascular occlusive disease in the eye or in such critical sites as the cerebral or the coronary arteries appears not to be common. This group, however, has not yet succumbed to the atherogenic diet of the Western World which may be an important factor. I have, however, seen a patient develop bilateral branch retinal vein thrombosis after moving from sea level to a high altitude in Turkey. The patient in question had a haematocrit of 54 with no evidence of either primary polycythaemia or of lung disease.

It has been suggested that altered rheological properties of the blood may contribute to the pathophysiology of acute mountain sickness[18] and that exposure to high altitude for some weeks may cause a change in red cell morphology with many circulating red cells showing a similar abnormality to that noted in patients with abetalipoproteinaemia.[19]

Leukaemia

White cells too contribute to whole blood viscosity and in the leukaemias the white cell mass is probably an important factor in the genesis of leukaemic retinopathy[20,21] although thrombocytopenia and coincident anaemia are probably equally important.[14]

Another aspect of white cell behaviour is the ability of these cells to infiltrate tissues. In

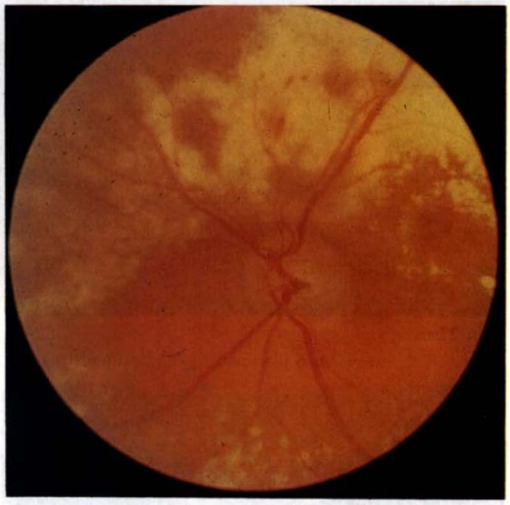

Fig. 21a

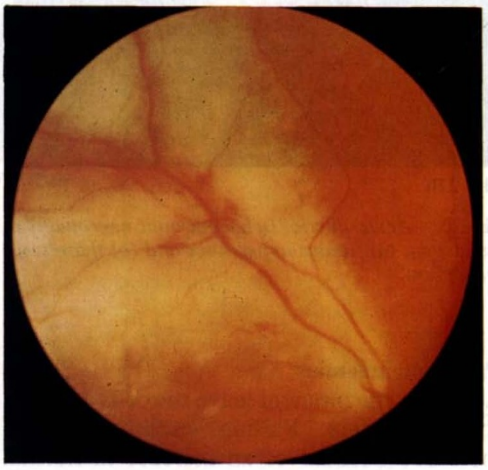

Fig. 21b

Fig. 21. *Retinal cellular infiltration in multiple myeloma (a) and Hodgkin's disease (b).*

the lymphoproliferative disorders cellular infiltration of the retina or the optic nerve head may be seen (Fig. 21). The physical effects of such infiltration in the optic nerve head may interfere with circulation to give acute anterior ischaemic optic neuropathy (Fig. 22). The condition is not uncommon as a manifestation of the lukaemias particularly in children.

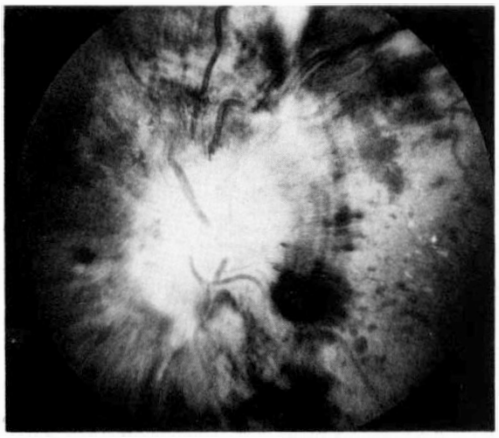

Fig. 22a

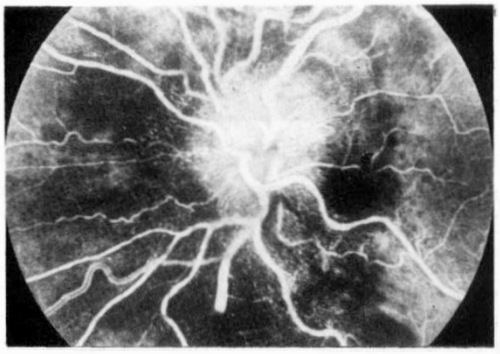

Fig. 22b

Fig. 22. *Acute anterior ischaemic optic neuropathy in leukaemia. (a) fundus appearance and (b) fluorescein angiogram.*

Paraproteinaemias

Let us for the moment leave the cells and turn to the plasma. Plasma viscosity can be increased because of an increase in normal constituents or from the presence in the plasma of abnormal molecules. Increased amounts of immunoglobulin and particularly of highly polymerised abnormal immunoglobulins such as are seen in multiple myeloma or in Waldenstrom's macroglobulinaemia give rise to the well known but relatively rare hyperviscosity syndrome[22] characterised by bilateral retinal venous engorgement and a very slow retinal circulation as revealed by fluorescein angiography (Fig. 23). Many years ago, Professor Ashton and I[23] showed that capillary endothelial cell proliferation and microaneurysm formation in the peripheral retinal capillaries were striking features of the hyperviscosity retinopathies and probably related to hypoxia (Fig. 24).

As is well known dysproteinaemic retinopathy can be normalised by plasma pheretic removal of the abnormal plasma proteins in multiple myeloma or macroglobulinaemia indicating the causal role of these proteins in the genesis of the retinopathy.[23,24]

Hyperlipidaemia

As already mentioned some forms of hyperlipidaemia are associated with raised plasma viscosity because of increased levels of large molecular weight lipiproteins. Increased blood viscosity may be an important factor in the aetiology of ocular vascular problems in hyperlipidaemia although, of course, narrowing of major vessels from degenerative vascular disease is common in this condition.

In my experience hyperlipidaemia may be associated with vascular insufficiency not only in the retina but in the choroid or the optic nerve head. The following patients are illustrative.

Case 1

A 52-year-old man presented with a sudden onset of blurred vision in the right eye associated with peripapillary swelling which settled to leave an area of choroidal atrophy (Fig. 25a). Vision was reduced to 6/36. Many of the retinal vessels showed patchy opacification. Fluorescein angiography showed what appeared to be a choroidal infarct near the disc (Fig. 25b). The main systemic abnormality was a severe hypertriglyceridaemia of 4.7 mmol/l with a moderate increase in cholesterol and elevation of pre-beta and betalipoproteins. Plasma viscosity was increased to 1.88 cPs. Carotid ultrasound was normal and the presentation suggested vascular insufficiency in the posterior ciliary arteries.

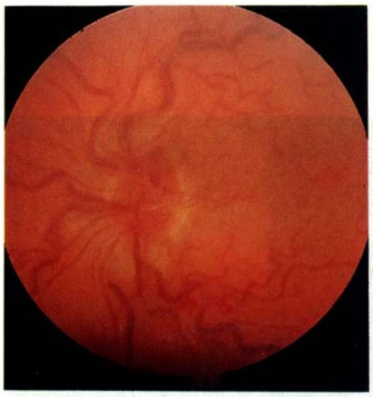

Fig. 23a

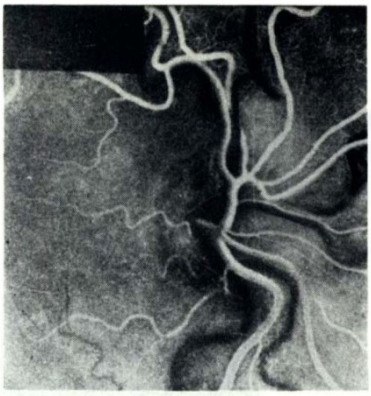

Fig. 23b.

Fig. 23. *Waldenstrom's macroglobulinaemia. (a) fundus appearance and (b) fluorescein angiogram.*

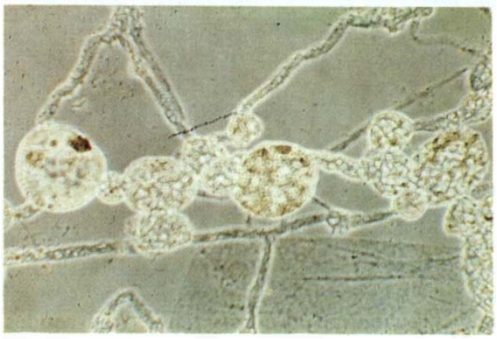

Fig. 24a

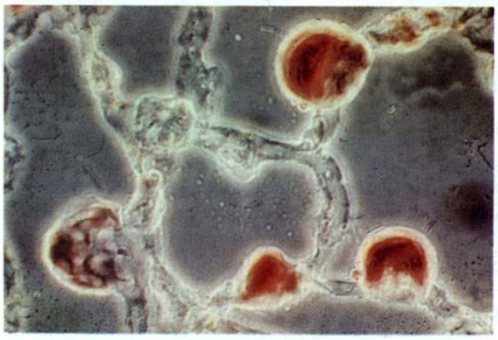

Fig. 24b

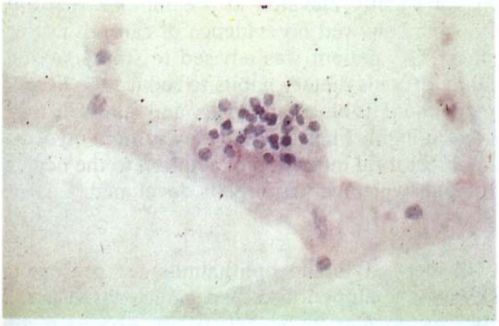

Fig. 24c

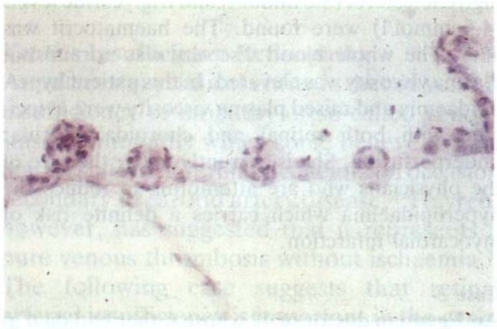

Fig. 24d

Fig. 24. *Trypsin digest preparation of the retina in macroglobulinaemia to show multiple retinal aneurysm formation (a, b, c) and in multiple myeloma (d) (preparation made by Professor N. Ashton). (a, phase contrast; b, stained Sudan III for fat; c, to show endothelial cell proliferation in an aneurysm (H & E); d, multiple capillary aneurysms in multiple myeloma (H & E)).*

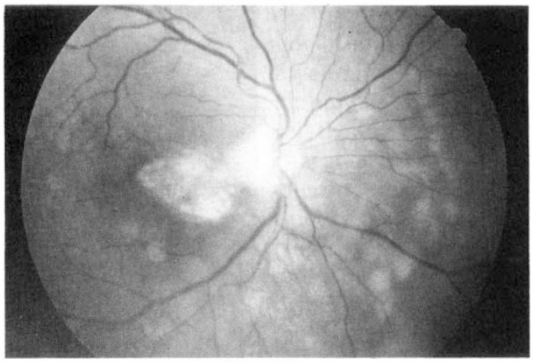

Fig. 25a

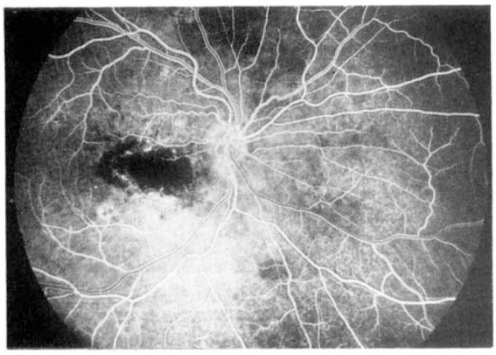

Fig. 25b(i)

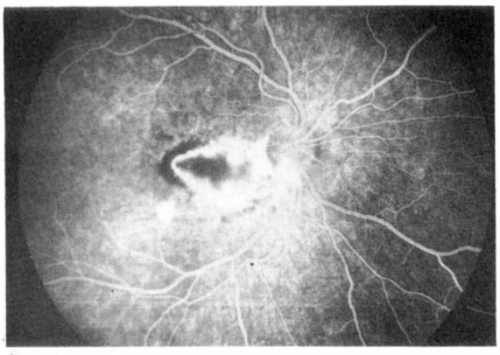

Fig. 25b(ii)

Fig. 25. *(a) fundus appearance and (b) fluorescein angiogram in a patient with a choroidal infarct associated with hyperlipidaemia.*

Case 2

A 54-year-old female patient was treated by laser in Denmark for what was diagnosed as juvenile disciform degeneration. On examination she had gross capillary underperfusion in the retina and subretinal neovascular membranes in each eye (Fig. 26). Full investigation ruled out sarcoidosis or other systemic inflammatory abnormality but once again high cholesterol (8.6 mmol/l) and triglyceride levels (4.5 mmol/l) were found. The haematocrit was 42.5. The whole blood viscosity was normal but plasma viscosity was elevated. In this patient hyperlipidaemia and raised plasma viscosity were associated with both retinal and choroidal vascular underperfusion. She is currently under the care of the physicians who are attempting to reduce the hyperlipidaemia which carries a definite risk of myocardial infarction.

Case 3

An Egyptian doctor of 42 whose father had died at the age of 49 from a myocardial infarction and whose brother had also had a myocardial infarction at the age of 42 suffered recurrent acute ischaemic optic neuropathy in each eye and evidence of retinal and choroidal vascular insufficiency. His haematocrit was 50 and whole blood viscosity was slightly raised at 6.09 cPs. Plasma viscosity at 1.65 cPs was just outside the normal range. Triglycerides were markedly elevated at 4.2 mmol/l and cholesterol slightly elevated at 7.8 mmol/l. Carotid ultrasound showed no evidence of carotid insufficiency. The patient was advised to stop smoking and to alter his dietary habits to reduce the hyperlipidaemia. His blood chemistry and family history makes it highly likely that he may suffer a myocardial or cerebral infarction in addition to the ocular problems which he has already developed.

Case 4

A 42-year-old Indian ophthalmologist presented with deeply cupped discs and glaucomatous field loss. Intraocular pressures never exceeded 17 mm/Hg. Triglycerides at 2.0 mmol/l and cholesterol

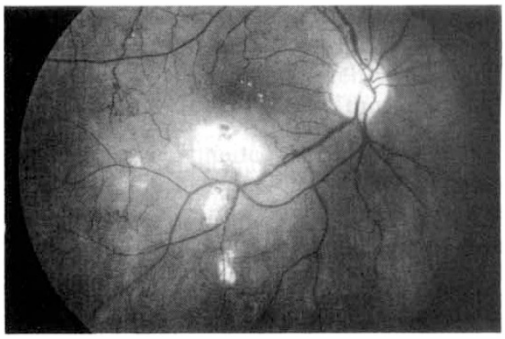

Fig. 26a

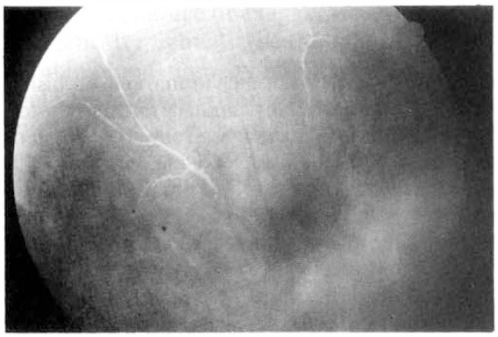

Fig. 26b

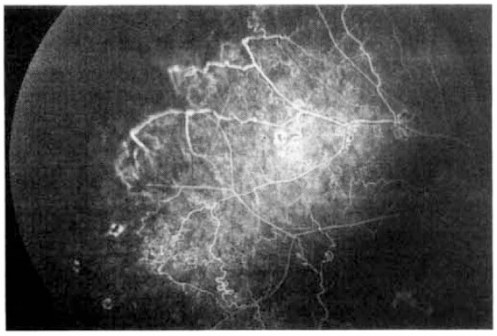

Fig. 26c

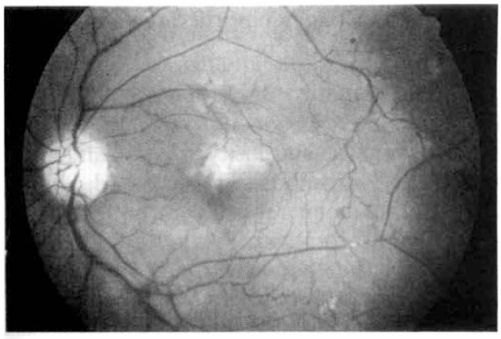

Fig. 26d

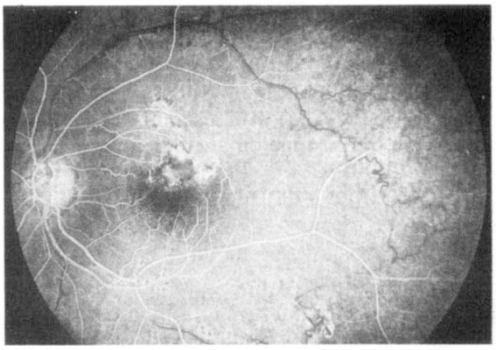

Fig. 26e

Fig. 26. *Fundus appearances and fluorescein angiograms in a patient showing widespread retinal and choroidal vascular insufficiency in association with hyperlipidaemia. (a) right fundus (the scars indicate previous laser therapy), (b) peripheral fundus right eye to show vascular occlusions, (c) fluorescein angiogram right eye to show gross vascular abnormality, (d) left fundus, (e) fluorescein angiogram left eye.*

at 8.4 mmol/l were both elevated as was plasma viscosity at 1.88 cPs. All other blood values were normal. As part of the therapy of his low tension glaucoma this patient has succeeded in normalising his blood chemistry by an appropriate modification of diet.

These four cases suggest that hyperlipidaemia associated with haemorheological abnormality may be present in various forms of ocular vaso-occlusion in relatively young patients. Whether the raised blood viscosity in these patients is important in the aetiology of the ocular problems remains conjectural. Occlusive vascular disease by reducing perfusion pressure may alter flow and shear forces so that abnormal rheology can play an important role in residual blood flow.

Venous Insufficiency Retinopathy

An interesting clinical entity is that of venous insufficiency retinopathy or so-called venous stasis retinopathy which some believe to be a manifestation of retinal ischaemia on occasion secondary to carotid artery disease.[25] Hayreh, however, has suggested that it represents a pure venous thrombosis without ischaemia.[26] The following case suggests that retinal arterial insufficiency is important in the genesis of venous insufficiency retinopathy.

Case 5
A young man of 34 suffered a loss of vision to 6/60 in the left eye after an attack of migraine. The fundus appearance was typical of 'venous insufficiency' retinopathy (Fig. 27a) with a significant prolongation of dye transit time on angiography (Fig. 27b) and a reduced intraocular pressure (12 mm/Hg as compared with 17 mm/Hg in the fellow eye). Vision recovered to 6/6 over the course of the subsequent week.

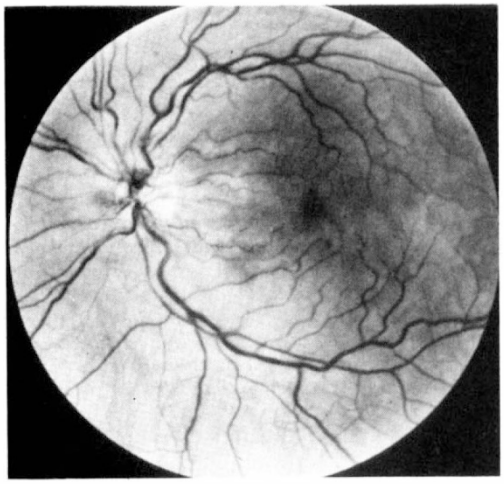

Fig. 27a

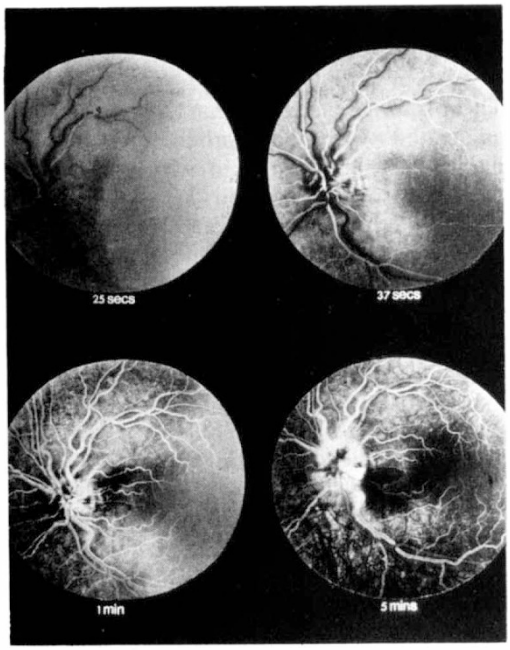

Fig. 27b

Fig. 27. *(a) fundus appearance and (b) fluorescein angiogram in a patient developing venous insufficiency retinopathy immediately after an attack of migraine.*

The onset of this patient's visual loss and the development of venous insufficiency retinopathy immediately after an attack of migraine suggests that the ocular abnormality had been precipitated by arterial spasm related to the migraine.

Abnormal blood rheology may sometimes play a role in the genesis of venous insufficiency retinopathy.

Case 6
A man of 74 suffered a branch retinal vein occlusion in the left eye followed by capillary underperfusion and vitreous haemorrhage from retinal neovascularisation. This was treated successfully with laser. Two years after the vein occlusion, vision in the right eye fell from 6/9 to 6/60 with the development of a venous insufficiency retinopathy. Dye transit on fluorescein angiography was grossly prolonged at over 150 seconds. He received four infusions of low molecular weight dextran and simultaneously the vision improved to 6/18 and dye transit rapidly fell to normal values. Eight months later he had a further episode of visual loss to 6/24 and on this occasion blood rheology was investigated and found to be abnormal. In particular blood viscosity at low shear rates (47 cPs) was grossly elevated. On four successive days 250 ml of blood were withdrawn and replaced on each occasion with 0.5 litre of low molecular weight dextran. Visual acuity improved to 6/9 and blood viscosity and plasma viscosity showed a fall to the upper limit of the normal range.

The close correlation of whole blood viscosity and the severity of the venous insufficiency retinopathy in this case points to the importance of abnormal haemorheology in the genesis of the retinopathy.

Retinal Vein Occlusion

What about blood viscosity in established retinal vein thrombosis? Increased blood viscosity has been reported in patients with retinal vein thrombosis.[27] In a study reported by us some time ago[28] the mean whole blood and plasma viscosity were found to be higher among patients with retinal vein thrombosis than among matched normal controls. The

cause of raised viscosity in this group of patients was a raised haematocrit or an increased plasma fibrinogen level each accounting for roughly half of those cases with raised viscosity.

Of more significance is the fact that raised blood viscosity was related to the ischaemic complications of vein occlusion manifested either as capillary underperfusion or the development of neovascularisation.[28,29,30] It is not difficult to imagine that if vessels are narrowed or partly occluded raised blood viscosity may further embarrass the circulation and either induce or exaggerate any ischaemia present. It might also be thought that a reduction in blood viscosity might be of therapeutic value in relation to the outcome of retinal vein occlusion as regards ischaemia or neovascularisation. A prospective randomised controlled trial, the results of which we have reported,[31] has shown that reducing whole blood viscosity in patients with retinal venous thrombosis has a beneficial effect at 16 weeks as regards the development of retinal ischaemia or neovascularisation, but at one year the benefit is no longer demonstrable. Reduction of blood viscosity in our patients was achieved by a combination of bleeding to produce a standard haematocrit of 40 per cent and the administration of the drug Stanozolol which reduces plasma viscosity via its effect on plasma fibrinogen. Unfortunately this drug causes fluid retention and related side effects and is not well tolerated.

Other studies in which blood viscosity was reduced by haemodilution alone[30] or by pentoxyfylline and haemodilution[31] have shown some promise in relation to the outcome from retinal vein thrombosis.

Thus we have evidence that reducing blood viscosity is of benefit at least in the short term as regards the ischaemic complications of retinal vein occlusion. Unfortunately, at present we do not have an acceptable therapy for lowering blood viscosity in the long term.

Diabetic Retinopathy

There is general agreement that blood viscosity is increased in diabetes.[34] We have shown that the level of blood viscosity correlates with the presence or absence of diabetic retinopathy[35] and with the severity of retinopathy,[36] patients with proliferative retinopathy having the highest blood viscosity.

In diabetes we have looked not only at the whole blood and plasma viscosity but also at red cell deformability. Measurements carried out in the Royal Infirmary in Glasgow have shown that red cell deformability is decreased by 10 per cent in diabetics as compared with normals but this increased rigidity of the red cells in diabetics is not demonstrably more pronounced among those with proliferative diabetic retinopathy than among diabetics without retinopathy.[36] A recent study using a more refined method for determining red cell deformability appears to show, however, that red cells in patients with proliferative retinopathy are indeed less deformable than those from unaffected diabetics and certainly this has been a reported experience elsewhere.[37] Apart from red cell defor mability both whole blood and plasma viscosity are significantly higher in patients with proliferative retinopathy than in those with non-proliferative retinopathy. Indeed, there is a gradient in blood viscosity from normals through patients with uncomplicated diabetes, those with background retinopathy and finally those with proliferative retinopathy, the whole blood and plasma viscosity being successively higher in each of these groups. The increased blood viscosity in these cases is related to increased plasma fibrinogen but whether the increased viscosity plays a role in the development of the retinopathy or whether it is merely a marker for some other aspect of the disease is not known.

Raised blood viscosity in diabetes appears to be related to glycaemic control[38,39] and this may be one more reason for aiming at good diabetic control in diabetic patients.

Glaucoma

The last aspect of haemorheology I wish to consider is its possible role in the genesis of field loss in open angle glaucoma. There is a great deal of evidence that intraocular pressure is not the only factor of importance in relation to field loss in this condition and indeed in patients with open angle glaucoma field loss frequently continues even when the

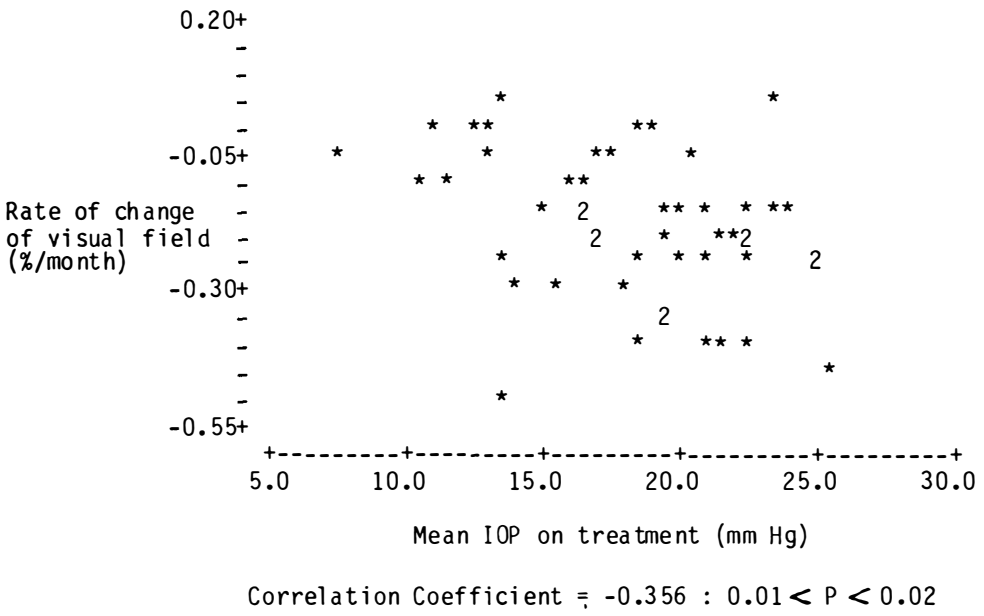

Fig. 28. *Correlation between the level of intraocular pressure on treatment and the rate of visual field loss in open angle glaucoma. There is a significant correlation P = <0.02 but the correlation coefficient is low 0.3 (based on statistical data provided by Mr. Redmond J. H. Smith).*

pressure has been normalised by surgery.[40,41] Redmond Smith in his Lang Lecture[42] quantified field loss in open angle glaucoma treated medically or surgically and showed that continuing field loss occurred in both groups of patients at a rate which did not correlate with the level of intraocular pressure. Using Redmond Smith's figures and with his help one can see (Fig. 28) that there is a positive correlation between the rate of field loss in open angle glaucoma and the mean level of intraocular pressure on treatment (P = <0.02). The correlation coefficient at 0.3 is, however, weak indicating that factors other than intraocular pressure are important. Vascular insufficiency has been suggested as a cause of field loss in glaucoma and with the known association of retinal vein occlusion with glaucomatous cupping it is interesting to consider the possibility that a common factor such as abnormal haemorheology might be important in both conditions.

In a recent study increased blood viscosity was found in both low tension and high tension open angle glaucoma.[43] We in Glasgow are looking actively at blood rheology in relation to field loss in open angle glaucoma.

So far we have studied 52 patients with glaucoma and 26 normal subjects. As yet the study is incomplete but there is an interesting trend towards higher blood viscosities at low shear rate with increasing severity of field loss (Fig. 29). Red cell deformability is marginally poorer in glaucoma patients than controls but the scatter of results in both groups is wide and at present the differences are not significant.

If, however, the trend towards raised viscosities in relation to visual field loss in glaucoma is confirmed then blood viscosity may be one additional factor acting with intraocular pressure and other factors not yet identified which together determine the rate at which a patient with open angle glaucoma will lose field.

Interestingly, we have found no correlation between the extent of field loss at the start of treatment and the subsequent rate of field loss on therapy arguing against the commonly held view that cupping of the disc itself is a risk factor for further field loss in glaucoma.

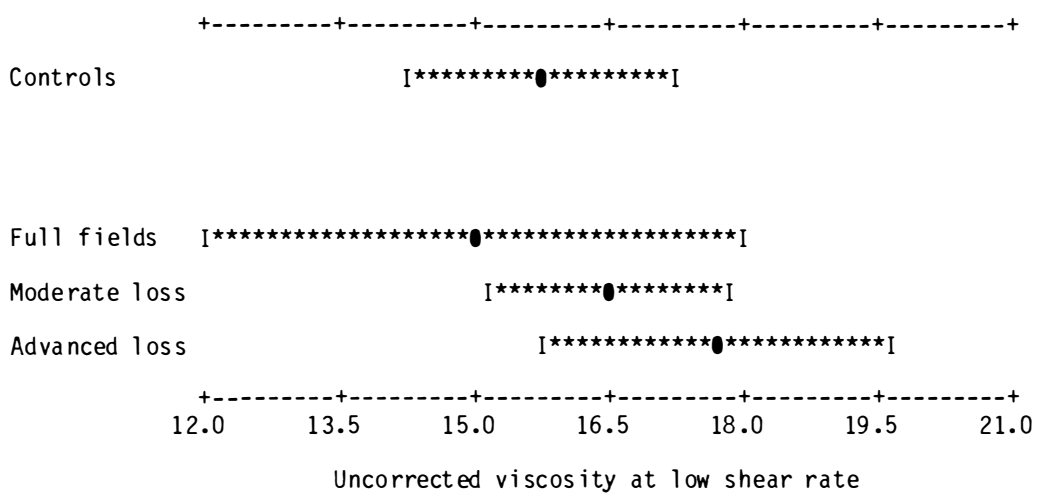

Fig. 29. *Whole blood viscosity at low shear rate and visual field loss in open angle glaucoma. There is a trend towards higher blood viscosities in patients with greater degrees of visual field loss.*

Conclusions

If I were to sum up my present views on the role of abnormal haemorheology in disorders of the eye, it appears obvious that severe overtly abnormal haemorheology as is seen in the dysproteinaemias, polycythaemias and the leukaemias may be both life threatening and sight threatening as also is the case with some of the sickling disorders. The treatment of these conditions with appropriate systemic measures not only may save or prolong life, but additionally restore vision.

In acute ischaemic optic neuropathy, venous insufficiency retinopathy and ocular circulatory disorders associated with hyperlipidaemia, blood viscosity may play a covert aetiological role. In these conditions acute reduction of viscosity by haemodilution or by other means may be sight saving. In the case of hyperlipidaemia measures to reduce blood lipid levels may have an immediate beneficial effect on blood circulation by virtue of a reduction in blood viscosity and a longer term effect on vessels or on blood coagulability which may prevent further ocular problems or more importantly death from myocardial infarction or stroke.

In established retinal vein thrombosis some of the ischaemic complications might be averted were we to have available a well tolerated and efficacious viscosity lowering drug. In diabetes and perhaps in open angle glaucoma abnormal blood rheology may be one of many factors playing a part in the aetiology of the retinopathy or of the field loss. As yet the role of blood rheology in these conditions has not been quantified, nor do we know if normalisation of blood rheology is beneficial.

The elucidation of the rheological and biochemical abnormalities which may underlie a wide variety of ocular vascular disorders is time consuming and difficult and as ophthalmologists we sometimes forget that the patient attending our out-patient practice is more than just a vehicle for bringing a pair of eyes to the ophthalmologist. In this day of holistic medicine it is appropriate to consider the whole patient. Bowman gave his name not only to layer of the cornea but to part of the kidney. His interests were wide and in considerable contrast to the super-specialisation which is the order of the day. We can still learn from Bowman and other famous physicians who remembered the importance of the whole patient in the maintenance of ocular integrity.

I should like to thank the many people who over the years have stimulated my interest in haemorheology, Dr. d'A. Kok and the late Dr. H. Lehmann of Cambridge and particularly Dr. G. D. O. Lowe of Glasgow. I should also like to thank the many ophthalmologists who have referred cases to me. I am

indebted to Drs. G. Trope, L. Esakowitz and E. Alvarez who contributed to the clinical studies reported in the Lecture and to Mr. J. H. Redmond Smith of Moorfields Eye Hospital, London, for allowing me access to his glaucoma statistics. I should like to thank Dr. G. D. O. Lowe for Figures 5 and 9, Dr. N. F. Johnson for Figure 6 and Professor W. R. Lee for Figures 10 and 17. Figures 24a to d were originally prepared by Professor N. Ashton for a joint publication in *J. Path. and Bact.* The scanning electronmicrographs including the resin cast study of the retinal and choroidal capillaries were prepared by Mrs. D. Aitken. Dr. D. Allan undertook the statistical analyses, Mrs A. Currie prepared the illustrations and the manuscript was typed by Mrs. J. Murray to all of whom I am grateful.

The work was supported by a grant from the Frost Foundation which is gratefully acknowledged.

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