CLINICAL SIGNIFICANCE OF HAEMORHEOLOGY

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Ischaemia of various organs or tissues is the commonest pathological process in severe and fatal diseases. It has always been widely assumed that ischaemia is the result of either cardiac failure or narrowing of the arteries. Haemorheology is concerned with the third possibility, that ischaemia may also be due to an abnormality of the flow properties of the blood. Whilst we all accept in everyday life that an increase in the viscosity of a fluid will decrease its flow rate, it is only in the last decade that doctors have begun to accept the analogous possibility in relation to blood. This is despite the fact that as medical students we have all been taught Poiseuille's famous formula relating blood flow to the driving pressure, the fourth power of the vessel radius and its viscosity (Figure 1). But now haemorheological considerations are beginning to influence clinical practice. For instance the management of young men with essential hypertension, older men with inoperable arteries and ischaemic pain of the legs, young girls with Raynaud's phenomena or patients with chronic cerebral ischaemia, have all changed or been modified by our better understanding of haemorheology. Often these and many other patients are now receiving more appropriate and more effective treatment: the young man's hypertension may simply be due to the compensation of his heart to an increased blood viscosity and peripheral resistance and the vicious cycle of established hypertension may be arrested by timely use of drugs normalising red cell deformability; similarly the older man with intermittent claudication may be allowed to walk further; and the young girl's Raynaud's symptoms may be totally abolished by a course of plasma exchange. The examples multiply, for instance the patient awaiting routine surgery with a pre-operative haemoglobin of 11 grams percent will avoid unnecessary and potentially dangerous blood transfusion. Simple laboratory investigations, like the haemoglobin concentration or the erythrocyte sedimentation rate, which have been routine for decades, have taken on a completely new significance through our better understanding of haemorheology. The most important property of blood is that it should flow, and yet we have been obsessed for decades by the results of studies of blood carried out in test tubes. Undoubtedly, the two principal reasons why haemorheology,

Fig. 1 — Doctor G. L. M. Poiseuille and the famous formula he published in 1846.

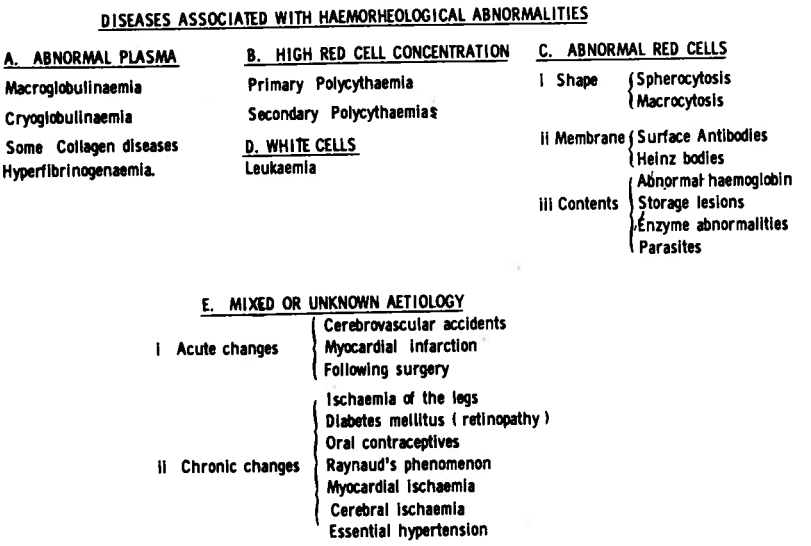

Fig. 2 — Classification of diseases associated with haemorheological abnormalities.

or the physical flow properties of blood, have been ignored for so long are that at operation or in the post mortem room atherosclerosis of the arteries is clearly visible whilst it is only recently that the measurement of blood viscosity has become possible. The measurement of blood viscosity, and even more recently of red cell deformability, have now given us quite a new insight into the factors determining blood viscosity and how it may be altered in disease. But even now many standard texbooks of medicine do not contain terms like viscosity, let alone red cell deformability in their index. Blood had traditionally been studied under static conditions, frequently on microscope slides, where Bessis described them as flattened, brilliantly coloured cadavers.

The viscosity of whole blood was the first haemorheological concept to require widespread clinical acceptance and a large number of diseases where a haemorheological abnormality has been described can be classified on a partly aetiological basis depending on which of three primary determinants of whole blood viscosity is at fault. That is whether the hyperviscosity is due to an abnormal plasma protein concentration, a high haematocrit or decreased red cell deformability (Figure 2). This latter group can be subdivided on the basis of whether the increased red cell deformability is due to the shape of the cell, a membrane or cytoplasmic abnormality. For the most part these are classical haematological diseases and relatively rare. They

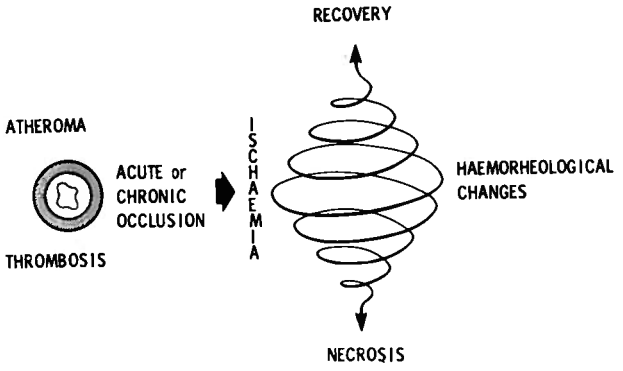

Fig. 3 — Diagramatic representation of the interaction between haemorheological determinants.

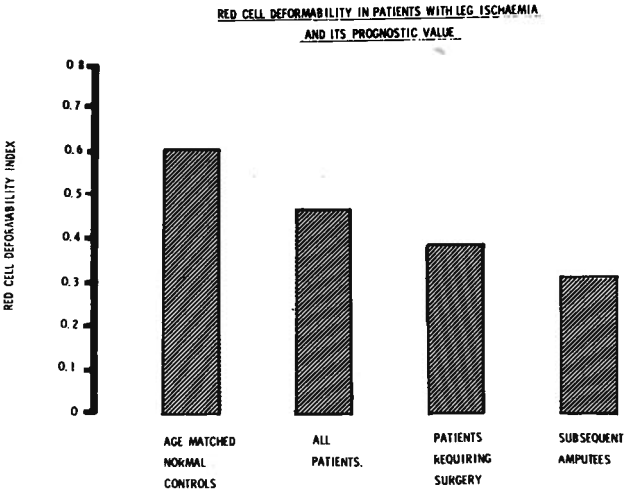

Fig. 4 — Red cell deformability in a group of patients with ischaemia of the legs, related to their subsequent progress.

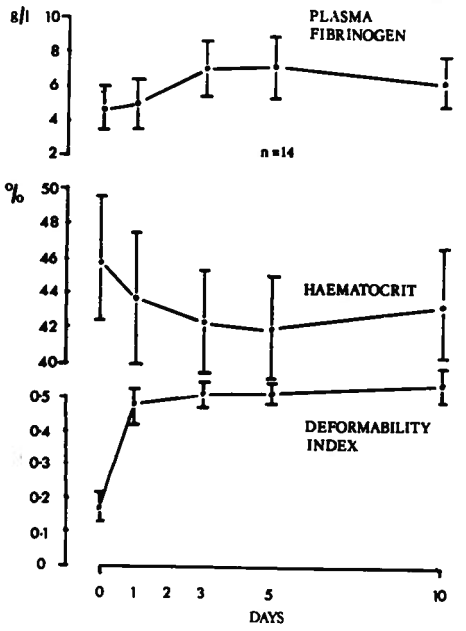

Fig. 5 — Haemorheological changes in a group of patients following acute myocardial infarction.

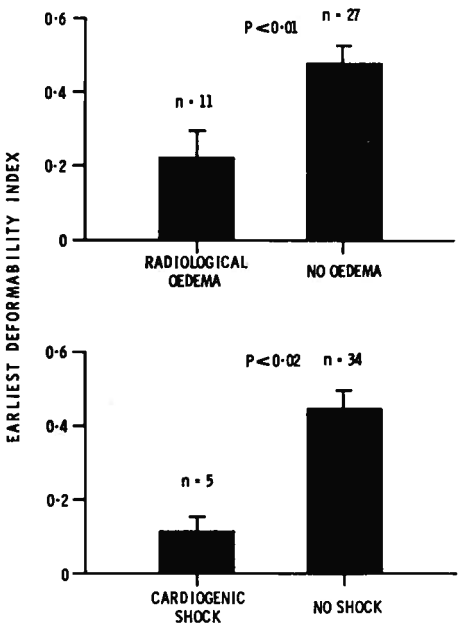

Fig. 6 — Prognostic significance of early chages in red cell deformability following myocardial infarction.

could be termed primary hyperviscosity or sclerocythaemic states because of the clearcut cause and effect relationship. By contrast there is a last group of much commoner diseases associated with circulatory abnormalities where a raised whole blood viscosity or decreased red cell filtrability have also been demonstrated, but the contribution of the various factors is not known. These could be termed secondary hyperviscosity or sclerocythaemic conditions because of the more complex relationship between the ischaemia of the tissues and the haemorheological abnormality, which will be discussed later. Our concept of haemorheology has somewhat altered in the past year or two and has now given rise to the concept of an amalgam of a number of haemorheological determinants, which interact with each other in a complex manner, illustrated diagramatically in Figure 3. For instance, whole blood viscosity is not only dependant on the viscosity of plasma and the deformability of the red cells, but also on concentration and aggregability of the red cells. The plasma proteins, in particular fibrinogen, are known to determine plasma viscosity and also the aggregability and possibly the deformability of the red cells. Even more recently we have come to appreciate the role of the plasma proteins adsorbed into the red cell. In fact a protein surface layer probably covers not only the particulate components of the blood but also the vessel wall, all the components of what has been termed the blood-vessel organ. The rheological properties of these surfaces must mediate all cell — cell and cell — vessel wall interactions and may thus play a central role in haemorheology. Furthermore, in considering the possible long term pathological role of haemorheological factors the effect of shear stresses on red cells and directly or indirectly on platelets has recently assumed importance.

The role of haemorheological abnormalities in four common conditions will be used to illustrate some of the variously complex interrelationships between haemorheology and clinical manifestation of circulatory disease. Diabetic microangiopathy illustrates well the complex interaction between haemorheological and other haematological and biochemical pathological processes.[1,2] Several studies have now shown a correlation between increased blood viscosity, decreased red cell filtrability and the clinical severity of the microangiopathy. These changes in turn can be related to increase in the plasma viscosity, which appears to be largely a fibrinogen effect, the actual blood glucose level and to the metabolic change in the diabetic red cell such as an increase in 2,3-DPG and decrease in ATP. Perhaps the most intriguing suggestion has been that insulin itself has a direct effect on red cell deformability. This could explain most simply the correlation between the quality of metabolic control of diabetes, HbAlc and the deformability of red cells. Recent work in diabetics has also thrown up the fascinating finding of a direct link between the erythrocyte deformability and platelet aggregation. In trying to assess the significance of red cell deformabily measurements in general, but perhaps particularly in relation to diabetes, it may be worth while considering the possibility that we are assesing a wider and more generalised cellular change in the body. We cannot easily

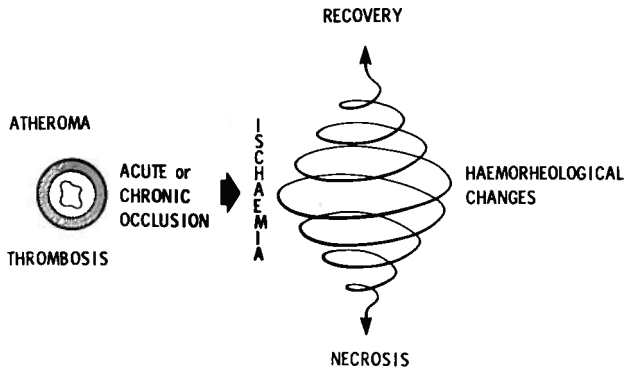

Fig. 7 — Diagramatic representation of the vicious circle which may develop between ischaemia and haemorheological changes. The direction in which such a cycle will spiral may be amenable to therapeutic influences.

sample the fixed cells of the body, the endothelial or the glomerular cell for instance; the red cell is naturally the only cell in the body which is amenable to reasonably atraumatic and easy sampling and at the same time comes into contact with all the other cells. The changes in the red cell membranes which we observe may be important because they reflect similar types of changes in other cells we cannot sample. The red cell may be a kind of circulating computer tape which we can sample and attempt to decode.

Essential hypertension is an example of a common disease, not previously considered to be of haematological origin, but where recent clinical evidence suggest that a haemorheological defect may well play a primary and direct aetiological role. Several studies now have shown that decreased red cell deformability and increased viscosity may be a primary defect in essential hypertension.[3] By definition, essential hypertension is diagnosed in otherwise healthy young people where none for the classical causes of hypertension can be demonstrated. An increase in the viscosity of these patiens' blood may well be a primary mechanism, as the only way a healthy heart could maintain a normal cardiac output when faced with an abnormally viscous blood would be by increasing its output pressure. Treatment of the hyperviscosity at this stage may well prevent the development of the later irreversible changes associated with established hypertension. Although this may appear to be a very new concept there has been for some time quite solid evidence that haemorheological factors may play an important role in the development of hypertension. The Framingham study[4] has shown that the haemoglobin level of a large apparently healthy population was a significant predictor of hypertension several years later. The most plausible explanation is an effect of the increased whole blood viscosity which, although not measured directly, must have paralleled the increased haemoglobin concentration.

Neither diabetic microangiopathy nor the early stages of hypertension are characterised by vessel narrowing. But ischaemia of the legs producing intermittent claudication or rest pain is undoubtedly principally caused by stenosis or occlusion of the major arteries, due to atherosclerosis and thrombosis. The haemorheological connection here is rather intriguing as there is some circunstantial evidence that haemorheological abnormalities may play a part in arterial thrombosis, and of course we know that repeated thrombosis is thought by many to be an underlying process in atherosclerosis.[5] These possible links fall into four groups. Firstly, there is the solid evidence from epidemiological studies, like the Framingham, Stockholm and more recently from Northwick Park that in an apparently normal population a high red cell or fibrinogen concentration are the best predictors, that is the most significant risk factors, for the subsequent development of cardiovascular or cerebrovascular accidents.[4] Secondly, the localisation of these arterial defects at characteristic sites seem to be largely determined by haemodynamic considerations, which are of course intimately connected with the rheological properties of the blood.[6] Next there is experimental evidence, supported by recent clinical findings directly linking haemorheological abnormalities, particulary decreased red cell deformability, with thrombosis through an effect on platelet aggregation.[1] Finally there is evidence, mentioned in more detail later, that irrespective of the initial cause of the thrombosis and any subsequent infarction, its progression and development seem to be closely related to the accompanying haemorheological changes.[7] It is perhaps for reasons such as this that many of us have found not only a significant abnormality in whole blood viscosity and red cell deformability in patients with symptoms and signs of ischaemia in the legs, but also a much more interesting correlation between the degree of abnormality and the patient's clinical progress. For instance when the red cell deformability was measured in an undetected group of claudicants the dregree of abnormality was greatest in the patients who in the subsequent years were found to require an amputation.[8] (Figure 4). This not only the most important underlying principle and justification for the haemorheologically aimed nonsurgical treatment of these patients but it also has a particular bearing on the work of the vascular surgeon. Both in arterial reconstructions and in the healing of amputation stumps we have found that success or failure is closely related to the haemorheological status of the patient at the time of operation. For instance in a series of distal amputations for ischaemia in diabetics, the immediate pre-operative haematocrit was a better predictor for success or failure of healing than the severity of the diabetes, quality of control, fever, white

cell count or a number of other plausible alternatives.[9] Is is therefore important for the vascular surgeon to be aware of the haemorheological status of his patient, even though the immediate problem he is tackling is a mechanical fixed stenosis. Two patients may be arteriographically equally suitable for reconstruction, but the patient who has a hyperviscosity state may not only derive less benefit from his operation, but is also more prone to the risk of rethrombosis and complete failure.

The fourth and last clinical condition to be considered will illustrate the types of pathophysiological role played by haemorheological abnormalities in an acutely ischaemic condition, myocardial infarction. Although we are ignorant of the changes immediately preceding the clinical syndrome of myocardial infarction once it has begun, the principal primary haemorheological changes are haemoconcentration, increased plasma fibrinogen concentration and decreased red cell deformability[7] (Figure 5). These changes all tend to cause an increase in blood viscosity, although the time scales are different. The changes in red cell deformability are the most rapid, reaching a minimum in 6 to 18 hours and usually returning to a baseline value within 24 to 28 hours of the onset of the first symptoms. The plasma fibrinogen and whole blood viscosity changes continue for several days although this is also dependent on the rate at which the haemoconcentration is reversed by intravenous fluid therapy. It would seem reasonable to suppose that the changes in the flow properties of blood during the evolution of a myocardial infarction play a role in its pathological and clinical outcome. And indeed there is clinical evidence that the severity of the earliest chages in the flow properties of the blood do relate to prognosis. Figure 6 shows that the eleven patients who developed pulmonary oedema had a significantly lower filtrability index than the patients who did not. Similarly with the five patients who developed clinical features of cardiogenic shock, whith a systolic blood below 100 milimetres for mercury and oliguria. Two of the three patients who died within two weeks of admission had red cells on admission which could not be filtered at all.

This last example of acute haemorheological changes highlights the problem whether these changes are a cause or a consequence of the ischaemia. The current hypothesis is that haemorheological changes are both a cause and a consequence of the ischaemia. Local changes in ischaemic tissue, such as hypoxia, hyperosmolarity, acidosis, the accumulation of metabolites and depletion of ATP have all been shown to impair the deformability of red cells. There may therefore be set up a vicious cycle, illustrated diagramaticall in Figure 7, where ischaemia reduces the deformability of red cells locally, which in turn further impair

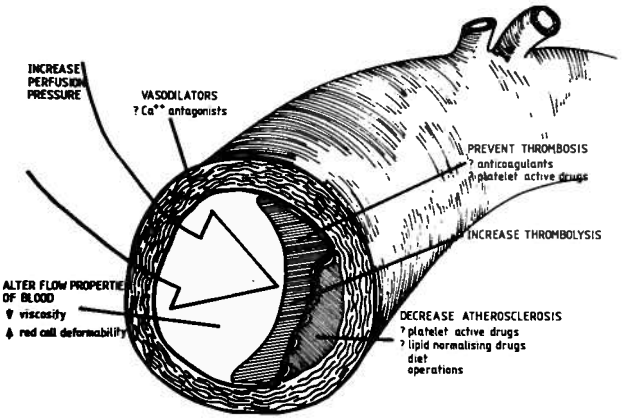

Fig. 8 — Possible approaches to the treatment of poor blood flow in major arteries.

the circulation increasing the severity and extent of the ischaemia. This hypothesis would explain the strong prognostic significance of the early chages in red cell deformability following acute tissue infarction, as observed for instance following myocardial infarction. The same may be true following acute cerebral infarction, although this has not yet been tested. Such vicious cycles may spiral one way towards necrosis or built-in physiological compensatory mechanisms may help it spiral towards recovery. This balance may exist in both chronic and acute ischaemia, and it may be another logical point for therapeutic intervention.

Clinicians became interested in haemorheological active drugs because of the increasing evidence that haemorheological abnormalities play a part in the pathophysiology of many common circulatory diseases. Their interest increased further when it became apparent that such agents may also be used in the management of ischaemia due primarily to other causes. The potential for haemorheological treatment has much wider implications than simply in conditions where a haemorheological abnormality has been detected. Figure 8 illustrates the various possible therapeutic approaches to the problem of ischaemia due to arterial disease. Surgical removal of the mechanical stenosis has only limited application. Of the non-surgical techniques, there is little evidence that atheromata can be dissolved, nor that established thrombi can by lysed. Preventing further thrombosis is of course reasonable, but generalised systemic vasodilatation or increase in central perfusion pressure can be positively dangerous. We are therefore left with the possibility of altering the flow properties of the blood, so that more blood will flow down the same narrowed channels.

The rheological properties of the blood may be improved by influencing any one of its primary determinants discussed previously. Normovolaemic hae-

modilution, the modern resurrection of the venesection practised by our predecessors for over two millenia, is rapidly gaining in popularity. It has been used in the treatment of ischaemia in virtually all parts of the circulation. Although it involves a reduction in the oxygen carrying capacity of the blood, there is little doubt that the increase in flow velocity due to the lowered viscosity more than compensates for this and that the overall oxygen delivery is improved. This may only be true in patients with ischaemia due to vascular disease. The evidence in favour of therapeutic normovolaemic haemodilution has been reviewed elsewhere.[10] The second direction of therapeutic attack may be on the plasma, not only decreasing its own viscosity but more importantly decreasing its propensity to cause red cell aggregation. Lowering the plasma fibrinogen concentration is the obvious strategy. Unfortunately, unless this is very high, there is no safe long-term pharmacological technique for achieving this. For short periods it can be achieved with one of the defibrinogenating agents, and it has been shown that in selected cases of intermittent claudication this can produce short term benefit.[11] Therapy aimed primarily at the plasma may also be beneficial in terms of an indirect improvement in the red cell deformability, which is the third primary haemorheological determinant. There is evidence suggesting that in some circumstances reduced red cell deformability may be secondary to changes in the plasma. This approach to the treatment of both the plasma and red cell abnormality is well illustrated by the technique of plasma exchange or plasmapheresis. This has been used most extensively in the treatment of Raynaud's phenomenon (12).

From the pharmacological point of view, improvement in the deformability of the red cells seems the most promising approach at the present. Such an agent must be safe long term and could have the role of protecting the red cell against the effects of ischaemia, this breaking the vicious cycle described earlier, or it may have a direct effect improving red cell deformability where this is a primary object. Previous presentation summarised our knowledge about the factors which may make a red cell abnormally rigid, and theoretically a number of different agents may improve the red cell deformability. But from the clinical viewpoint, we already have drugs that have been shown to improve red cell deformability in vivo and some have been shown to produce significant clinical improvement in patients with ischaemia affecting the legs and the brain. It would appear that a whole new generation of pharmacological agents are already available or are being developed for the treatment in circulatory impairment using a new haemorheological approach. In conclusion, the rheological properties of blood are now recognised to be as relevant clinically as its respiratory, biochemical, or clotting properties. The ability of the blood to transport oxygen, metabolites and control the milieu interieur of the body, all depend on its continuing ability to flow, that is its haemorheological properties. Blood viscosity and the deformation of red cells are physiological facts. We can now probably measure these functions accurately and demonstrate with some certainty a pathophysiological role for them in a number of circulatory diseases. But whatever we may think of the extent or accuracy of our current knowledge about it, whatever we may think of its present clinical relevance, physicians and surgeons concerned with any aspect of the circulation should not, and cannot, any longer ignore it.

REFERENCES

1. JUAN, I., BUONOCORE, M., JOUVE, R., VAGUE, P., MOULIN, J. and VIALETTES, B.: Abnormalities of erythrocyte deformability and platelet aggregation in insulin-dependent diabetics corrected by insulin in vivo and in vitro. Lancet i: 535-537 (1982).

2. BARNES, A. J., LOCKE, P., SCUDDER, P. R., DORMANDY, T. L., DORMANDY, J. A., SLACK. J.: Is hyperviscosity a treatable component of diabetic microcirculatory disease? Lancet ii: 789-791 (1977).

3. CHIEN, S.: Decreased red cell filterability in essential hypertension. Communication at the Second European Conference on Clinical Haemorheology: London (1981).

4. KANNEL, W., GORDON, T., WOLF, P., McNAMARA, P.: Haemoglobin and the risk of cerebral infarction: The Framingham Study. Stroke 3: 409-420 (1972).

5. DORMANDY, J. A.: Haemorheological aspects of thrombosis. Brit. J. of Haematology 45: 519-522 (1980).

6. GOLDSMITH, H. L. and KARINO, T.: *In* Quantitative Cardiovascular Studies (Ed. N. H. C. Hwang, D. R. Gross and D. J. Patel) University Park Press, Baltimore, pp. 289-351 (1979).

7. DORMANDY, J. A., BOYD, M., ERNST, E.: Red cell filterability after myocardial infarcion. Scand. J. Clin. Lab. Invest. 41, Suppl. 156: 195-197 (1981).

8. REID, H. L., DORMANDY, J. A., BARNES, A. J., LOCK, P. J. and DORMANDY. T. L.: Impaired red cell deformability in peripheral vascular disease. Lancet 666-667 (1976).

9. BAILEY, M. J., JOHNSTON, C. L. W., C. J. P., SOMERVILLE, P. G. and DORMANDY, J. A.: Pre-operative haemoglobin as predictor of outcome of diabetic amputations. Lancet 168-1970 (1979).

10. DORMANDY, J. A., YATES, C. J. P. and BERENT, G. A.: Clinical relevance of blood viscosity and red cell deformability including newer therapeutic aspects. Angiology 236-242 (1981).

11. DORMANDY, J. A., GOYLE, K. B., REID, H. L.: Treatment of severe intermittent claudication by controlled defibrination. Lancet 625-626 (1977).

12. DODDS, A. J., O'REILLY, M. G. J., YATES, C. J. P., COTTON, L. T., FLUTE, P. T. and DORMANDY, J. A.: Haemorheological response to plasma exchange in Raynaud's syndrome. Brit. Med. J. 2: 1186 (1980).

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