HYPERVISCOSITY IN HYPERTENSION

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You think (do you not?) that you have only to state a reasonable case, and people must listen to reason and act upon it at once. There is little hope of dissuading you; but has it occurred to you that nothing is ever done until everyone is convinced that it ought to be done, and has been convinced for so long that it is now time to do something else?

And are you not aware that conviction has never yet been produced by an appeal to reason, which only makes people uncomfortable?

If you want to move them you must address your arguments to prejudice and the political motive ... if you do not become effective before you cease to want anything to be done - why, what will be the good of you?

- F.M. Conford
Microcosmographica Academica, 1908

For Hippocrates ... the purpose of venesection was mainly to reduce the substance of the buffy coat in the vascular system of the patient. Thus the doctrine of the fibrin as the *materia morbi,* which was the corner stone of humoral pathology, introduced bleeding in the medical treatment ...

By bleeding, phlegm could be removed before it had congealed and set fast. The organism was thus spared the double effort of first melting the congealed phlegm and then getting the melted masses out of the body.

... the immediate effect of bleeding must often have been miraculous. Especially in pneumonia, venesection gave the patient relief in a way which no other treatment could bring about. For the physician the mitigation of the sopor, of the dyspnoe, of the cough and often of the fever was taken as an experimental proof of the correctness of the therapy.

- R. Fahraeus
The Four Fluids of Antiquity

Estratto da ATTI del XIV Congresso Internazionale di Storia della Medicine, Vol. II, p. 1, 1954

Preface

The role of this book is to describe the role of blood viscosity, red cell rigidity and other viscosity factors in the aetiology of 'essential' or primary hypertension. Hypertension is today one of the primary risk factors in mortality and morbidity from cardiovascular causes. Notwithstanding the world-wide studies of hypertension, its mechanism remains obscure. This is perhaps not so amazing, as the study of vascular content, the blood itself, has been neglected.

Blood cannot be viewed as an inert fluid in the development of hypertension. Just as the rheology of blood and its elements, as well as blood coagulation and thrombus formation, are involved in the aetiology of ischaemic disorders, so their contribution to aetiology of hypertension can be anticipated by researchers. Thus, data on haemodynamics of hypertension were reviewed to extract data implicating blood rheology in the aetiology of hypertension.

In this book a rheological hypothesis is proposed in which blood viscosity and rigidity of red cells play a role in the development of hypertension. A hypothesis is presented in which a twin regulatory mechanism, based on viscosity controllers, plays a role in hypertension. Older data and observations are reviewed to provide evidence for such hypothesis.

The realization that blood viscosity must be of importance in circulatory disorders had become clear to me by 1962. Subsequent work in our laboratory, and in other laboratories, indicated that increased viscosity of blood must play a role in poor health and disease. Then I developed the conviction that the viscosity of blood must be regulated in some manner; that an autoregulatory mechanism for blood viscosity must exist; and that rheology of the red cell must play a crucial role in vascular resistance and in the essential hypertension.

I presented the concept of autoregulation of blood viscosity and of visco-receptors for the first time at the Annual Renal Conference in Sydney, in 1975. The basic premise did not, at first, appear to be properly substantiated, as

a longitudinal relation between rigidity (decreased deformability) of the red cell and viscosity of blood appeared to be lacking. Suddenly I realized that the longitudinal relationship did exist and, what is more, that its evidence had been in my hands for some time, in results obtained from tests on malignant melanoma patients who died of metastases. These data showed increasing elevation of the red cell rigidity, and simultaneous decreasing of blood haematocrit and even greater decreasing of the viscosity of whole blood as the moment of death came nearer and nearer.

If blood viscosity and red cell rigidity do play a role in arterial blood pressure and in essential hypertension, then there should be a positive relation between arterial blood pressure and blood viscosity (especially when measured at high shear rates), and also between arterial blood pressure and the red cell rigidity. Indeed this was obvious in our studies of patients with chest pains and severe coronary artery occlusions; in joint studies with Girolami on patients with essential hypertension; in our studies on such patients; and in the studies on hypertensive diabetics.

One could thus expect that a decrease of blood viscosity and/or a decrease of rigidity of red cells would lead to a decrease of the arterial blood pressure. Some evidence for this came purely by accident, when we studied submaximal work output in patients, many of whom were on beta blockers. We found that (at least some) beta blockers reduced blood viscosity and rigidity of the red cells; and additional evidence was obtained by a review of the literature and reinterpretation of the results described.

A review of the literature on essential hypertension brought to light several studies in which viscosity of blood (or one of the viscosity factors) played a role, and this evidence was collated to support my basic premise: that hypertension aetiology must include abnormality of the blood viscosity factors, and especially rigidity of the red cell.

I must confess that for many years I was so influenced by my colleagues assertions that renin, angiotensin, aldosterone, etc., were the main features of the essential hypertension, that I did not consider seriously the role of blood viscosity - although, on theoretical grounds, one should have expected such a correlation. I hope that this book will convince specialists in the field of hypertension that rheology of blood plays a crucial, if so far a very neglected role.

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The book is directed at all researchers in hypertension; physiologists, cardiologists and bioengineers alike. It should provide an experimental, and possibly therapeutic, tool for the physicians interested in treatment of hypertension.

The introduction of a rheological component into the fundamentals of circulation should not only allow a better understanding of aetiology of disease but also lead to more efficient therapy.

About the author

Dr Leopold Dintenfass, a clinical haemorheologist, started his studies in blood viscosity and its role in disease at Sydney Hospital and in the Department of Medicine, University of Sydney, in the early 1960s. Over a period of twenty years, he held the following posts:
Senior Research Fellow at the Department of Medicine, University of Sydney;
Senior Research Fellow of the National Health and Medical Research Council of Australia;
Commonwealth Visiting Professor, University of Strathclyde, Glasgow, and Senior Research Fellow, Glasgow University Department of Medicine at the Royal Infirmary, Glasgow;
Research Associate, Hadassah University Hospital, Jerusalem;
Honorary Consulting Biorheologist, and Head of Haemorheology and Biorheology Unit (Professorial Unit), Sydney Hospital.

Dr Dintenfass has lectured at many international congresses, ranging from cancer and haematology to bioengineering, biorheology and cardiology; and was visiting lecturer at such universities and hospitals as the Mayo Clinic, Stanford University, Harvard University, the University of Oregon, the University of Texas, Columbia University and the University of Milan.

His two monographs on blood viscosity and its role in clinical medicine were published in 1971 and 1976, respectively.

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Contents

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Chapter 1
Basic Aspects of Blood Rheology

Introduction

The term 'rheology' describes the science of flow and deformation of all matter, including that of such fluids as blood, protoplasm, synovial fluid, ink, lubrication oils, etc., and 'solids' such as bone, steel, concrete, etc. The branch of rheology that deals exclusively with blood and blood vessels is called 'haemorheology'. This, in turn, is divided in two branches: one correlating the molecular, colloidal and cellular structure in blood or blood vessels, and deformation and/or the flow of blood, with the biochemical components of blood or vessels; this is called 'molecular haemorheology' or 'microrheology of blood' ('microhaemorheology'). The branch of haemorheology dealing with the problems of patients and disease is described as 'clinical haemorheology'. Both form two sides of the same coin.

In principle, the field of rheology is divided also into two branches. 'Phenomenological rheology' (or 'macrorheology') is the rheology that treats a material as a continuum; it is characterized by experimental rheological parameters, and the microstructure is not considered. 'Microrheology' is the rheology in which account is taken of the microstructure.

Viscosity is a measure of internal friction. The coefficient of viscosity (or more exactly, the *first* coefficient of viscosity, as there are many more coefficients - although when viscosity is discussed it is usually the first coefficient that is referred to) is the ratio of the shear stress to the shear strain rate in laminar flow.

This book deals with the microrheology (or molecular rheology) of blood in hypertension, with specific considerations given to the role of the red cells or aggregates of red cells and/or platelet aggregates whose presence under certain pathological conditions may lead to, or enhance, hypertension. The condition of 'hyperviscosity' may lead to hypertension. Blood hyperviscosity

(Dintenfass 1976b) can be due to elevation of any one of the blood viscosity factors: elevation of plasma viscosity, elevation of haematocrit, elevation of the degree of aggregation of red cells, increase in the internal viscosity and rigidity of the red cells, etc. Blood hyperviscosity can be accompanied by an increase in the viscosity of whole blood, but can be present in spite of normal or even decreased viscosity of whole blood. The crucial role of blood hyperviscosity is apparent in the microcirculation. The effect of increased rigidity of the blood cells or of the presence of microthrombi, microemboli or other products of blood coagulation, is amplified by the 'inversion phenomenon' in the microcapillary flow.

In human circulation, blood flows through a series of vessels of diminishing diameters but the total cross-section of these vessels is progressively increasing. Finally, in the enormous network of capillaries, blood flows through tissues bringing nourishment and taking away metabolites. Water, electrolytes, gases, proteins, carbohydrates and fats are being continuously exchanged between the blood and the tissues. The vascular system not only serves for irrigation or collection of refuse, but is also a highway for the transit of cells and chemical agents required to defend the integrity of the circulation and thus life of the individual. The continuation of an adequate flow of blood becomes a crucial factor in the function of the body. The flow of blood is controlled by a number of mechanisms, or agencies, including the rheology of blood itself.

The two main lines of our studies, blood rheology and dynamic blood coagulation (Dintenfass 1971b, 1976b, 1977c, 1979b) resulted in an insight which now permits the questioning of some established ideas. Thus, for instance, the role of the rheology of the red cell in the control of the circulation has been largely overlooked, the main attention having been given to vasodilatation or vasoconstriction. The old belief into capillary 'collapse' receded now as Fung et al (1966) have shown that the bore of a capillary is relatively constant, the capillary walls are relatively rigid, and capillaries might even be considered as 'tunnels' in a rigid matrix. The action of some drugs, purporting to have a vasodilator action, may indeed operate via an effect on the rheology of the red cell (Dintenfass 1977e).

I directed attention to the implications of the quantitative nature of the internal viscosity of the red cell on the viscosity of whole blood (Dintenfass 1962c, 1965e, 1968a, 1970c) and to its implication on the architecture of the

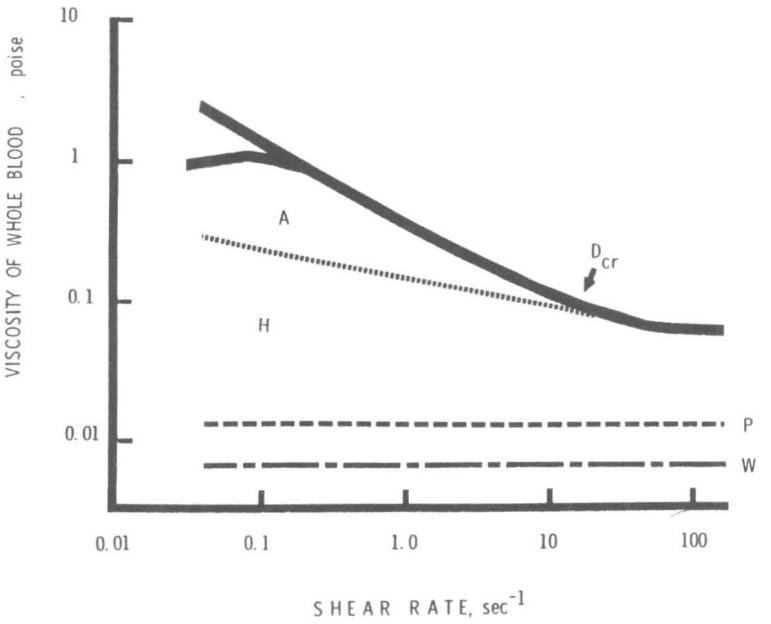

FIG. 1. Rheological schema of viscosity of whole blood. Apparent viscosity of blood is plotted against shear rate. The full line corresponds to the viscosity of whole blood; the arrow (D_{cr}) indicated the critical shear rate at which disaggregation of red cells takes place; the fork in the curve (left) shows possible viscosity patterns at low shear rates (the horizontal one due most likely to sedimentation of red cells). Area 'A' limited by dotted line indicates contribution of the red cell aggregates. Area 'H', limited below by broken line P, shows contributions of the packed cells (note that this contribution decreases with increasing shear rates); line P indicates viscosity of plasma (this line being true for all normals and most patients); line W corresponds to viscosity of water. Blood is thixotropic.

red cell membrane (Dintenfass 1964b, 1969b). Both, the cell interior and the cell membrane, must be highly fluid - under normal conditions.

The primary parameters of arterial blood pressure might include increased rigidity (decreased fluidity) of the red cell, presence of rigid aggregates of blood cells, on occasions an increased viscosity of the whole blood, all coupled perhaps with a malfunction of the viscosity control mechanism. In order to comprehend these systems, a short review of the basic factors of blood viscosity is in order.

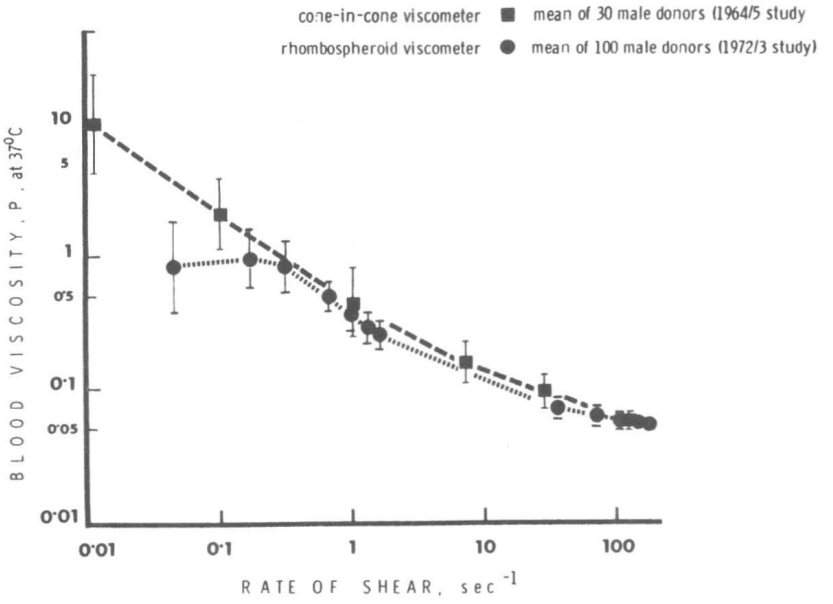

FIG. 2. Viscosity of whole blood in normals, measured by two different techniques. Dots show mean values obtained by means of the rotational rhombosperoid viscometer using anticoagulated (EDTA) blood, while squares indicate mean values obtained using the cone-in-cone viscometer and freshly-shed (not anticoagulated) blood.

Blood is a very complex fluid. Although the whole blood might exhibit viscosities in the order of 100- to 1000-fold higher than water at near-zero flow velocities, at high flow velocities it might show a viscosity of less than twice that of water. (See Figs 1 and 2). The complexity of blood rheology is due to the influence on the viscosity of whole blood of a series of simultaneous processes: (a) a reversible aggregation of the cells, which is usually responsible for the greater part of viscosity and thixotropy of blood at low shear rates and low flow velocities; (b) a shear-rate-dependent deformation and internal viscosity of the red cell and other blood cells (the concept of internal viscosity including the contributions of the actual interior of the cell and of the membrane of the cell); (c) volume fraction of the red cells (haematocrit): the effect of haematocrit on blood viscosity will depend on the apparent internal viscosity and deformability of the red cells, on the ratio of the apparent internal viscosity of the red cell to the viscosity of plasma,

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