THE RHEOLOGY OF BLOOD, BLOOD VESSELS AND ASSOCIATED TISSUES

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DAVID R. GROSS

and

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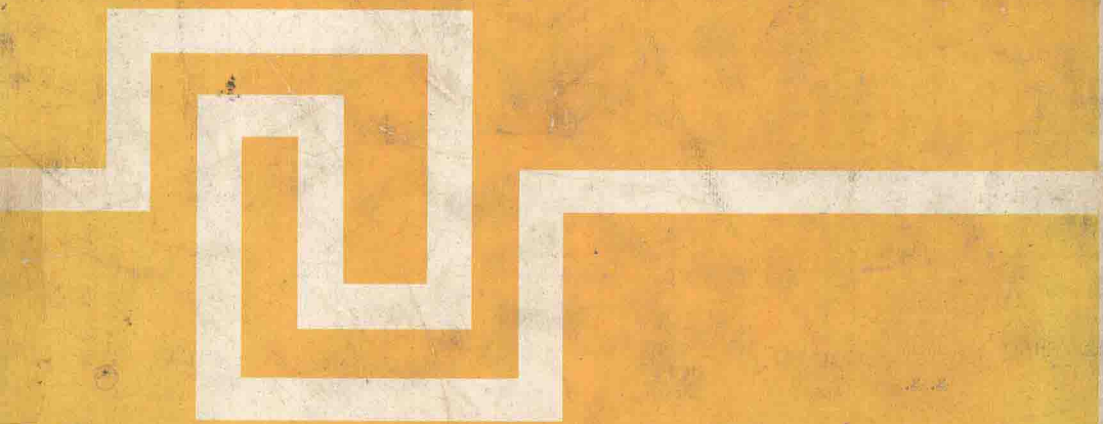

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DEDICATION

The scientific affairs division of the North Atlantic Treaty Organization annually sponsors advanced study institutes which cover a wide range of scientific topics. This text is a result of the second such ASI in which N.H.C. Hwang and D.R. Gross collaborated as organizers. The institute was held in Houston, Texas for two weeks in March and April of 1980 and was entitled: "Biorheology: Physics of Biological Tissues".

The general format of these institutes is tutorial. Lecturers are selected on the basis of their recognized expertise and world-wide reputation in the subject of their presentation. Participants are selected on a competitive basis with special emphasis on representation from all NATO countries. Young investigators with proven credentials in relevant areas of research are chosen with near equal distribution between life and physical sciences. These participants live and work together with the lecturers for the entire two week period, including many evening sessions. Many strong friendships are formed and professional alliances made. In the past, these alliances have resulted in high calliber collaborative research efforts, and we believe that this trend will continue.

We feel privileged to edit this text. We thank the NATO Scientific Affiars Division for their continued support. We dedicate this text to the NATO:ASI concept and to all the participants whose interest, enthusiasm, and attention made the whole experience worthwhile.

DRG, NHCH

PREFACE

Rheology is defined as the science of the deformation and flow of matter. The chapters in this text all have a common perspective, the study of the physical behavior of the systems being discussed. Although some of the topics may seem to be far removed from one another the authors are united in their approach. They all share a common interest in explaining the behavior of biological tissues in terms of physical laws.

The book has been divided into three parts. The five chapters included in Part I have a common theme, the clinical significance and applications of hemorheology. Although many statements made, particularly in the first two chapters, may cause some eyes to raise and provoke considerable comment, these opinions should be brought out into the open and given a fair scientific review. The seven chapters in Part II all deal with specific aspects of blood rheology. The authors of these chapters are all investigators of international reputation, and the chapters reflect the state of the art and science of their various topics. Part III contains chapters which discuss the rheology of the microvasculature, conduit blood vessels, and some associated tissues including the skin. We intentionally invited, and include in this section, Dr. Lanir's input on rheological behavior of the skin becuase it is our belief that some of his techniques and insights can be extended to problems in vascular tissue rheology.

THE RHEOLOGY OF BLOOD, BLOOD VESSELS, AND ASSOCIATED TISSUES

Contents:

Part I

THE CLINICAL SIGNIFICANCE OF HEMORHEOLOGY

PERSPECTIVES IN HEMORHEOLOGY 1980: AN INTERDISCIPLINARY SCIENCE RETURNING TO THE CENTER OF MEDICINE

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ABSTRACT. Hemorheological thinking is gaining ground in medicine and surgery - primarily due to pragmatic results rather than due to the general acceptance of a coherent theory. In contrast to a popular belief, hemorheology is not a modern asset of medicine - but rather a foundation of the oldest medical theory (humoral pathology). The link between modern hemorheology and the practical basis of the humoral pathology is described in pursuit of ideas originally laid down by FAHRAEUS. In an attempt to bridge the language gap between theoretical hemorheology and practical medicine, a semantic system centered around the non-dimensional term "relative apparent fluidity" is presented. Hemodynamic and biochemical abnormalities and their quantitative effect on relative apparent fluidity of blood are presented to illustrate the practical and heuristic potential of this semantic concept.

1. INTRODUCTION: THE PRESENT TREND OF HEMORHEOLOGICAL THINKING MEDICINE, PHARMACOLOGY AND PHYSIOLOGY

The present impact of hemorheological research on the theory and practice of medicine is primarily the consequence of convincing therapeutic results rather than of the general acceptance of a comprehensive theory. These pragmatic results were obtained by various remedies that measurably affect the "viscosity" of blood. In the 1960ies, this tendency was initiated by the introduction of low molecular weight dextran solutions in almost all fields of medicine and surgery. In the 1970ies, the rheological effects of

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+) Supported by Deutsche Forschungsgemeinschaft through Sonderforschungsbereich 109 (Artificial Organs) Aachen

defibrinogenating enzymes such as Streptokinase, Ancrod (or Arvin) and Defibrase were utilized primarily by angiologists in the therapy of tissue ischemia following peripheral arterial obliteration or occlusion. The late 1970ies saw the extension of the principle of hemodilution into medicine after this simple, inexpensive and safe procedure had stood the test of feasability, safety and effectiveness in cardiac surgery. Intentional, (whereever possible isovolemic) hemodilution was introduced into the treatment of ischemia in the cerebral (GOTTSTEIN, THOMAS), the ocular (WIEDERHOLT, KOHNER and DORMANDY) and the peripheral vascular bed (see paper by RIEGER, this volume). The obvious clinical success made it increasingly evident, that the hemodynamic effects of obliterative vascular disease processes (which are primarily located in the large arteries) manifest themselves in a qualitative and quantitative disturbance of the microcirculation. Furthermore, it became equally clear that there are independent reactions in the microvasculature, i.e. in the control of perfusion, of endothelial integrity and of exchange processes. Rheological factors are only a link in a large chain of other factors - yet soon it was shown that the rheological properties have a pivotal significance. The "flow properties" of blood and their characteristic (yet independent!) changes which occur in patients suffering from degenerative vascular diseases - can often determine critically the perfusion of decompensated microvascular provinces that are located behind an arterial stenosis or occlusion. It is reasonable to reason that the rheological behavior of blood component can become the limiting factor for the survival of tissues and microvascular integrity. Even if this is not true, rheological factors can be most easily manipulated by effective treatments. Restitution of blood flow via a restitution of blood fluidity then gives the other disease factors a chance to recover.

Furthermore, detailed analyses of the molecular and cellular factors responsible for the "anomalous" viscosity of the blood - i.e. its extreme variably as a function of the incident shear stresses and the tube radius - have led to a better understanding of the interaction of cardiovascular, biochemical, cellular and fluid dynamic factors in the microcirculation. The present paper attempts to summarize this action briefly by focussing on the phyiologically important aspects of "whole blood fluidity" and its possible disturbance in response to abnormalities of the factors listed above. Abnormalities in many systems are capable of interfering with the essential property of blood as a circulating organ, its ability to flow or "fluidity".

During the lastdecade, there has been a considerable extension of hemorheological thinking beyond the field of cardiovascular physiology and pathology.+ It has become increasingly clear that hemo-

+) For reasons of space, there are no references given in this paragraph. Any attempt to cite the relevant literature would lead to a bibliography of several hundred original papers and reviews.

rheological abnormalities are also pivotal for our understanding of such diseases as hemolytic diseases (where curtailment of red cell deformability has been generally been accepted as pathogenetic determinant and the common denominator of different ethiologically distruct forms of anemia), immunology (where the flow behavior of granulocytes, lymphocytes and platelets has been appreciated as pivotal to the understanding of defense and disease processes), haemostasiology (where not only the formation of red coagulae in static veins, but also the thrombotic deposition processes leading to white thrombi are being investigated under rheological and fluid-dynamic aspects). Pharmacology has discovered that many conventional drugs have significant hemorheological effects (or side effects). Therefore, possible hemorheological modes of actions of drugs are proposed, sometimes replacing traditional concepts (e.g. vasodilators are turned into compounds lowering blood viscosity, coronary dilators and antiphlogistic drugs are sold as platelet desaggregators etc.). In oncology, a new therapeutic strategy is aimed at interfering with the microcirculation rather than directly with the tumor cells growth. A prominent proponent of therapeutic hyperthermia and acidosis in tumor therapy (von ARDENNE) has taken hemorheological changes (loss of red cell flexibility) into the center of his pathogenetic concepts. Finally, hemorheological reasoning has entered the field of practical bio-engineering since it has become increasingly clear that the "blood trauma" as well as the thrombosis in all artificial organs is only understandable on the basis of a thorough hemorheological investigation of the details of the processes involved. The studies of platelet deposition in artificial organs have emanated very stimulating new concepts about the formation of atherosclerotic plaques and about the deposition of thrombotic material in branches, stenoses and stagnation points in arteries.

2. HISTORICAL PERSPECTIVE: HEMORHEOLOGICAL RATIONALE OF "HUMORAL PATHOLOGY"

One of the most striking flow "anomalies" of blood is its tendency to become more viscous when flowing slowly. It is generally accepted that 1) this phenomenon is based on red cell aggregation and 2) is more pronounced in disease states than under healthy conditions.
This idea is by no means new: it was a central part of the "humoral pathology" which dominated medicine from Hippocrates (who may have adopted it from even earlier Indian concepts laid down in Vedian scripts) to the middle of the 19th century. When R. FAHRAEUS, in my mind the greatest medical hemorheologist of our century, introduced the measurement of the sedimentation rate into the practice of modern medicine, he included in his thesis a lenghthy discussion of the hemorheological basis of humoral pathology (FAH-

RAEUS 1921). The classical theoretical framework of medicine from HIPPOCRATES to ROKITANSKI was based on very practical evidence that appeared to support the doctrine of the four humors and of their abnormal mixture in disease for all physicians and surgeons, that inspected the blood obtained from patients.

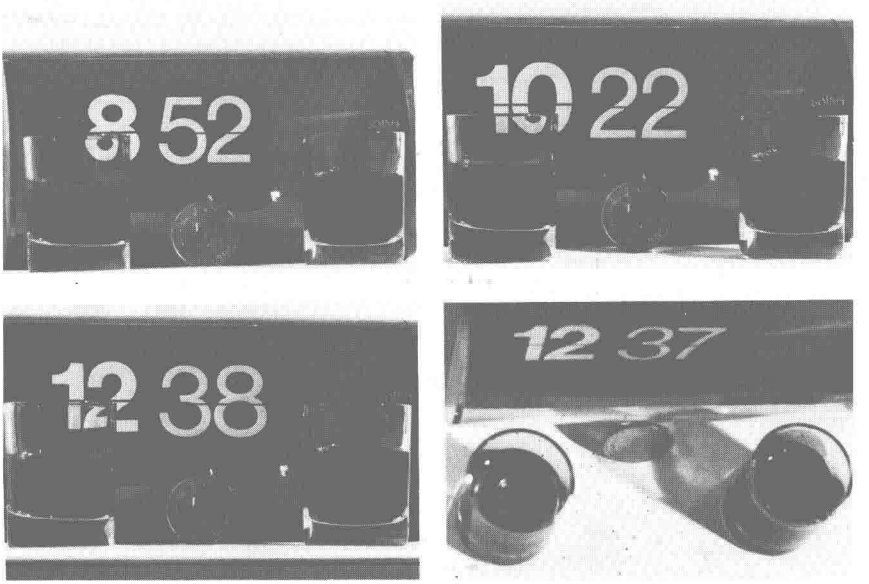

Fig. 1: Spontaneous coagulation of blood in a glass vial: comparison of normal blood and blood of a patient with high sedimentation rate. A:) 3 min. after the withdrawal of the blood, the sedimentation is clearly visible by the formation of a layer of platelet rich plasma. B:) After 2 hours, both samples are clotted and the ring shaped contraction of the clotted platelet rich plasma begins. After 4 hours, the classical "buffy coat" is visible at the top of the clot from a diseased person, but not in that of a normal subject (C and D, view from above)

As detailed in FAHRAEUS'thesis, and more recently by the present author elsewhere (SCHMID-SCHÖNBEIN 1980) the macroscopic appearance of clots obtained from patients' blood is significantly different from that of normal human beings. Owing to the much more rapid sedimentation of the aggregated blood in patients, the red cells separate from the (platelet rich) plasma before the latter

clots. After the clot in the platelet rich plasma (PRP) retracts, a typical whitish layer, the "buffy coat" appears on top of the sedimented red cell button - the characteristic "crusta inflammatoria". In the blood of healthy people without sedimentation, the fibrin, platelets and red cells form one solid coagulum, i.e. a redish-purple mass surrounded by clear serum (Fig. 2).

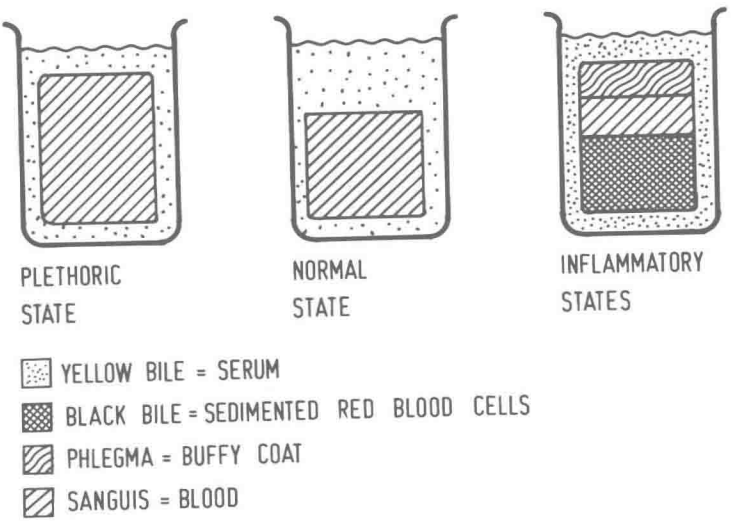

Fig. 2: Schematic representation of the macroscopic changes that can be seen in normal, plethoric and inflamed blood. For details see text.

Since we know from the old medical literature that blood was taken from patients during phlebotomy, and since the striking macroscopic differences between the two types of clots can be readily reproduced today, we can easily re-examine the only test method available to the physicians until the turn of the century: macroscopic inspection of the blood clot (Fig. 1 and 2). And indeed, the blood clot of patients contains four clearly separable components:

1. the strongly deoxygenated red cells at the bottom appear macroscopically black (black bile = melanchol),
2. the buffy coat or "crusta inflammatoria" appears as a white elastic layer (phlegma),
3. the serum looks macroscopically yellow (similar to the content of the gall bladder, yellow bile) and

4. there is a thin layer of red material (sanguis) between the buffy coat and the red cell button.

The origin of the "black bile" was placed in the spleen - a readily understandable hypothesis from the stand-point of a macroscopic anatomist who saw that only the spleen contained a similar black material, namely the blood with hematocrit values up to 80% that is found in the red pulp or the splenic veins after splenic contraction. In the two component coagulum of the normal subjects, there was no sign of black bile nor a phlegma - and it is only too understandable that the old physicians came to the conclusion that the disease was caused by an abnormal composition of the blood or a "dyscrasia".

We can easily understand the early beginnings as well as the gradual development of a medical theory which was based on an experience that every physician or surgeon had or has: patients do have an elevated sedimentation rate - this result obtained in a WESTERGREN tube is just as regular as the appearance of a buffy coat and of deoxygenated, i.e. black blood in the coagulum. Both phenomena are, as was firmly established by FAHRAEUS, - the result of an abnormal composition of the plasma, in other words of a "dysproteinemia" - which is obviously the contemporary counterpart to the dyscrasia in classical humoral pathology.

The significance of the humoral pathology and its practical basis on the scientific thinking can not easily be overestimated. Humoral pathology was part of a more general philosophical system in which the Macrocosm was explained, by 4 elements with 4 elementary qualities (see Fig. 3, modified after ROTSCHUH). In ancient psychology, the 4 temperaments (sanguinic, choleric, melancholic and phlegmatic) were also attributed to the mixture of humors - a concept that even explains the usage of our present word "humour" in the sense of good spirits.

I do not intend to elaborate more details of humoral pathology: however, it is not worthy that the theory included the notion that abnormally mixed humors did not move adequatily in the veins (e.g. in inflammation). It must be stressed that even before the discovery of the circulation of blood, there was the concept of a nutrition of the tissue by a (unidirectional) motion of the blood from the liver to the periphery. In the HIPPOCRATIAN scripts, and especially in GALEN's writing, abnormal physical properties of the dyscrasic blood are taken as the cause of tissue malfunction. (for details see SCHMID-SCHÖNBEIN, 1980)

We can now also appreciate the rationale behind the practice of phlebotomy - or venae sectio - which represents the therapeutic consequences of the theory of humoral pathology. Phlebotomy, for which strict indications and counterindications were laid down, was done with the same objective that led to the use of defibrinogenating enzymes: to remove the faulty or noxious material - materia peccans - from the body. Plethora, the other important indi-

ation for phlebotomy besides inflammation, also leads to very characteristic changes in the clot (relative lack of serum due to very slow sedimentation of blood with a high hematocrit). There must have been some immediate beneficial effect of phlebotomy. We can deduce from the striking objective and subjective improvements of the circulation after defibrinogenation and hemodilution - which represent a modern day application of the idea to remove a "materia peccans" - that the ancient doctors (and their patients) must have seen beneficial effects. Thence, it is very likely that daily diagnostic and therapeutic experience was taken as the corroboration of the dogma of "humoral pathology" - which the medical students had learned in the universities.

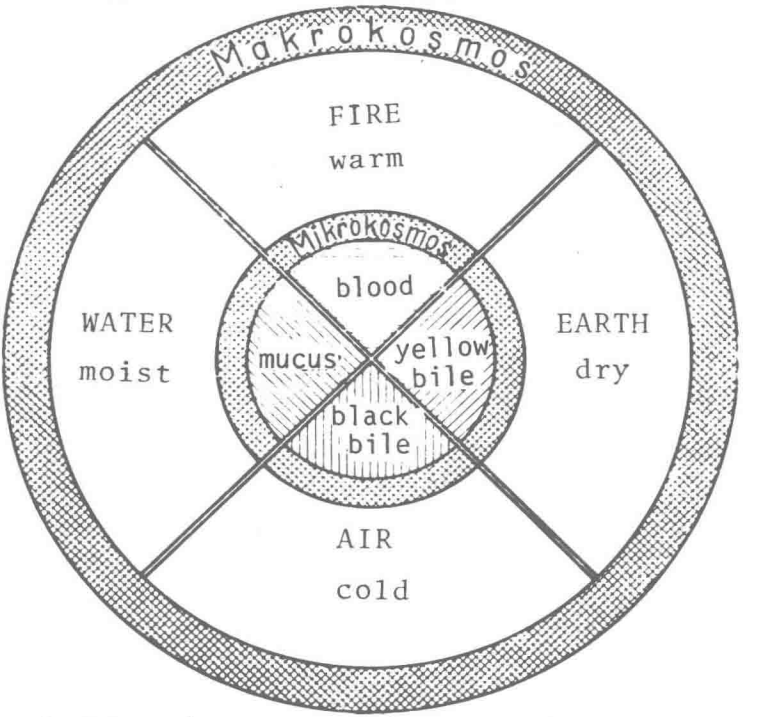

Fig. 3: Schematic representation of the integration of the humoral pathology into the natural philosophy of the Greeks: In the macrocosmos, 4 elements and qualities : fire (hot), earth (dry), air (cold) and water (moist) make up the composition of matter. In man, a microcosm reflecting the same basic scheme, the four elements are represented as four humours.
The adequate mixture ("Eukrasia") guarantees health, the abnormal mixture causes disease (dyserasia). The same scheme was applied to psychology, the temperaments (temperare = to mix) represent predominance of one quality. The terms: sanguinic phlegmatic, melancholic and choleric temperament have entered all European languages.

The discovery of the blood circulation, the practice of intravital microscopy and the development of the modern clinical medicine by HARVEY, MALPIGHI, SYDENHAM, BOERHAVE and HUNTER and most of all the development of the science of pathology (correlation of clinical symptoms to autoptic findings) by BOERHAVE and MORGAGNI deepened the impact of humoral pathology in the 17th and 18th century. It was clearly established that disturbances of the flow of blood were primarily responsible for a great number of inflammatory and (in modern terms) degenerative diseases in which

a) there was an abnormal blood clot as evidence of "dyscrasia" and in which
b) the symptons could be releaved by phlebotomy.

The 19th century saw the rather abrupt end of humoral pathology. ROKITANSKI, in his famous "Handbuch der Pathologie" wrote a scholarly account of the rôle of a stagment blood in degenerative and chronic inflammatory disease, now based on the regular observation that in diseased organs the vessels were tightly stuffed with red cell masses. This part of his pathological theory still stands undisputed - and the experimental pathologists of the 19th and the early 20th century extended research into the "stasis" phenomenon, which ROKITANSKI had attributed to an intravascular loss of blood fluidity. His attempt to explain tumors also on the basis of humoral pathology prompted VIRCHOW's harsh criticism - and at the same time it marked the victory of cellular pathology over humoral pathology as a concept.

FAHRAEUS attempt to rehabilitate humoral pathology failed - despite the great success of his test of measuring the suspension stability of blood. It is interesting to note that the established historians of medicine never took up FAHRAEUS scholarly account of the practical basis of humoral pathology. Against his intention, contemporary historians of medicine cite FAHRAEUS as the discoverer rather than the rediscoverer of the rapid erythrocyte sedimentation in disease. FAHRAEUS also studied intravascular red cell aggregation; in the USA, his concepts were taken up by KNISELY and BLOCH who gave a new name ("blood sludging") to a very old, well established phenomenon: the simultaneous retardation and adhesion of blood cells in the microcirculation. When low molecular weight dextran solutions were introduced into medicine (s.p.1) it was advocated as a specific antiaggregating agent: This latter claim about its mode of action was soon refuted; this notwithstanding, this compound started the practical success of hemorheology on medicine and surgery. From the almostundisputed aggreement about the causes of the non-Newtonian blood (red cell aggregation responsible for high apparent viscosity at low shear stresses, passive red cell orientation, deformation and fluid-drop-like participation at high shear, especially in narrow tubes) the basis of a better theoretical framework in hemorheology has now been

laid. These microrheological facts and/or variables and the results of newly developped test methods for the assessment can now be integrated in a system of hemodynamic theories which predict the rôle of "viscosity factors" in the normal and the disturbed circulation.

3. PROBLEMS OF SEMANTICS IN HEMORHEOLOGY

In the majority of physiological, pathophysiological and clinical textbooks presently used in medicine and surgery, hemorheology is underrepresented. The extreme complexity of modern hemorheology and the orientation of most physicians to the chemical rather than the physical sciences pose serious semantic problemes which make the task of a post-graduate training in this field even more difficult. The specialists in hemorheology, in addition, face a didactic dilemma: While on the one hand they want to overcome a popular prejustice (which downgrades blood viscosity as unimportant) they must, on the other hand, strive to prevent a new misconception. It must be made absolutely clear from the start that there is no such thing as "the" viscosity of "the" blood. The well-known flow anomalies must rather be presented as a characteristic behaviour of the blood in responce to the differing flow conditions under which the blood moves or fails to move in the different blood vessels. Blood viscosity as measured in the conventional viscometers only applies to a relatively small number of larger blood vessels (diameter > 0.3 mm). In the vast majority of microvessels (4 - 300 µm), the viscosity concept in the sence of continuum mechanics is not applicable. Here, the flow of plasma and the "disturbance effect" of blood cells upon the plasma (see communication by GAEHTGENS) must be analyzed. This "disturbance effect" of the blood cells can, however, be quantified in non-dimensional form by computing the relative apparent viscosity, i.e. the ratio of the apparent viscosity of the blood and the viscosity of the plasma ($\eta_{rel} = \eta_{app}/\eta_{pl}$) (which is assumed to be a newtonian fluid). By the same token, however, the reciprocal value, i.e. the relative apparent fluidity ($\phi_{rel} = \eta_{pl}/\eta_{app}$ or ϕ_{app}/ϕ_{pl}) can also be computed and can be used for hemodynamic analysis in all types of blood vessels. In an attempt to integrate all presently known flow anomalies into a coherent semantic system. I propose to introduce the term "relative apparent fluidity" into the hemorheological discussion (v.i.).

Recent rexperiments by GAEHTGENS have shown that well-known flow anomalies of the blood are predominantly seen in mammalian and thence human blood rheology. They are the consequence of the "bipotential" properties of the non-nucleated red cells, which, in response to the incident shear forces, can be either deformed and oriented in a shear field and "participate" in flow or they can be aggregated and can then disturb flow of plasma very effectively.