

CLINICAL HEMORHEOLOGY

*Applications in Cardiovascular and Hematological
Disease, Diabetes, Surgery and Gynecology*

edited by

S. CHIEN

J. DORMANDY

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Preface

The task the editors have set themselves is to survey the field of clinical hemorheology from basic principles to up-to-date research. It is only in a new science like this that it is possible to span the whole field in a book of this size.

Hemorheology, as a new approach to the study and management of a wide range of circulatory diseases, is now beginning to appear with increasing frequency in general as well as specialized medical journals. Hemorheology is also just beginning to creep into the undergraduate medical curriculum. Therefore, the majority of graduate doctors are unequipped to assess the place of hemorheology in the overall framework of circulatory physiology and pathology or to assess its relevance to their everyday practice. It is hoped that this book will fill this gap.

The approach of the book is interdisciplinary. The first part deals with basic principles of blood flow, circulation and hemorheology. It has been written with the general doctor in mind, who has no special knowledge of hemodynamics and rheological concepts, terminology or methodology. To maintain the emphasis on practical clinical applications, all the chapters in the second part of the book have been written by clinical specialists practicing in the individual areas of disease. The book is so designed that clinicians may be able to read the relevant chapters in the second part of the book in isolation, using the basic science aspects contained in the first part of the book as reference chapters.

Because hemorheology is a new science, its precise place in clinical medicine and surgery is still controversial. With the help of this book readers will be able to assess for themselves the evidence available at the moment, as well as the rapidly expanding new clinical literature of the applications of hemorheology.

S. Chien
J. Dormandy
E. Ernst
A. Matrai

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1

Introduction: On the way to modern clinical hemorheology

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Clinical hemorheology embraces one of the main areas in the practice of medicine, and goes back to ancient times [1]. Modern clinical hemorheology is practiced in different fields of medicine and surgery, as dealt with in this book and indicated in its subtitle.

It may be considered rather extraneous to acquaint the Reader with certain personal memories in this introduction, but the development of modern clinical hemorheology is to some extent associated with them. I began my career in the biomedical sciences in 1932 on the purification of thrombin in Würzburg at the Institute of Physiology under the direction of Edgar Wöhlisch who, at that time, was the leading authority on blood coagulation in Germany. He assigned to me, a medical student in the sixth semester, the teaching of blood clotting and its disorders to my fellow students in the fourth and fifth semesters. What I could not understand and explain to them was the phenomenon of a markedly prolonged coagulation time and a normal bleeding time in hemophilia and, vice versa, a normal coagulation time and prolonged bleeding time in thrombocytopenic purpura. Wöhlisch could not explain these apparently paradoxical findings and merely thought that the platelets may have something to do with them.

In 1939, ten years after rheology was founded as an organized science in Washington D.C., I pursued my clinical hemorheological studies at the Hixon Laboratory of Medical Research at the University of Kansas Medical School. During this time, I studied hemophiliacs and my first report on thixotropy of hemophilic and heparinized blood was published two years later [2]. During my stay at this Institute, Lalic and I attacked the problem of bleeding time in normal subjects and hemophilic patients with a new method, which we developed [3,4], without changes in hemodynamic pressure. We found that bleeding into physiological saline at 37°C, after infliction of a wound in the end phalanx of a finger, resulted in a free flow of blood [3]. The Copley-Lalic bleeding time is a truly clinical hemorheological test which has not yet been widely used. In connection with this test, we developed the "clot resistance" test [3], named more adequately later "wound thrombus resistance" [4], made several minutes following the bleeding time by the application of a cuff-pressure below the systolic

pressure. Recurrence of bleeding from the wound inflicted for the bleeding time may thus be provoked. We found that the bleeding time measures the initiation of in vivo hemostasis while wound thrombus resistance, its maintenance [4]. In making the bleeding tests we observed several other phenomena which we described, including the seepage into saline of a whitish flow, named "lymph time" [3]. These in vivo hemorheological phenomena still need further exploration.

As in normal subjects, the Copley-Lalich bleeding time was found to be within 3 minutes in hemophiliacs [5]. However, the wound thrombus resistance was always impaired in hemophiliacs which explains the recurrence of bleeding even from small wounds [4]. Lalich and Copley [6] described an extra vivum clinical hemorheological test which measures clot firmness in special viscometer tubes, to which pressure is applied. Clot firmness was found markedly reduced with blood from hemophilic patients [6].

Two other in vivo clinical hemorheological tests, employing negative pressures, developed later, measure capillary or vascular fragility by petechial counts and detect capillary hemorrhagic diathesis with the so-called "ecchymosis test" [4,7,21].

During my stay at the Hixon Laboratory, we made studies on viscosity, yield value, thixotropy, dilatancy and age-hardening of blood, secured with different anticoagulants, from healthy human subjects. A modified falling ball or so-called "rolling ball" viscometer, used at different shearing stresses, permitted the determination of flow properties of blood systems [8]. These studies, which were among the first reported on the anomalous flow properties of blood, were published by Copley, Krchma and Whitney in 1942. This communication in the *Journal of General Physiology* was particularly welcomed by rheologists in different countries, and created an impact that ultimately led to biorheology as an organized life science.

In 1943, I was asked by the British Society of Rheology to act as chairman of a Symposium on the Application of Rheology in Medical Science, held in Oxford in 1944, which I could not attend because of the war. Several years later, I was invited to give a Plenary Lecture on "Rheological Problems in Biology" at the First International Congress on Rheology, held in Scheveningen, Holland in 1948. There, I introduced the term "biorheology" in a survey [9], the first of its kind, of biorheological, including hemorheological, observations and studies. I stated that "I am convinced that rheology will play a very important role in the biological sciences including medicine of tomorrow. As observations on the flow of blood helped initiate the science of rheology, it is my belief that from continued observations on other properties of this very special part of life, namely blood, and of blood constituents, a combination of the sciences of rheology and biology is bound to serve the well-being of our species" [9].

The term "hemorheology" was introduced for the rheology of blood and of the blood vessel wall in a lecture before the Society of Rheology at the 25th

Anniversary Meeting of the American Institute of Physics, held in Chicago in 1951. At that time, I defined hemorheology as being "concerned with deformation and flow properties of cellular and plasmatic components of blood in macroscopic, microscopic, and submicroscopic dimensions, and with the rheological properties of vessel structure with which blood comes in direct contact" [10]. Although I have done experimental research in different areas of the biomedical sciences, hemorheology became my main interest.

Modern clinical hemorheology is based on theoretical and experimental hemorheology as well as on clinical findings. Theoretical hemorheology is subdivided into two areas; one deals with theoretical rheological aspects, the other with mechanisms of physiological or patho-physiological processes pertaining to phenomena and findings in experimental and clinical hemorheology.

A strong impetus to the organization of modern hemorheology was given at a conference which I initiated, entitled "Flow of Blood in Relation to the Vessel Wall", held in 1958 at Charing Cross Hospital Medical School of the University of London, and organized with the physicist George W. Scott Blair of the Physics Department, National Institute for Research in Dairying, University of Reading. The success of this meeting indicated the need for further activities and drew the attention of the Faraday Society. Subsequent discussions between F.J.W. Roughton, FRS of Cambridge University, R.G. Macfarlane, FRS of the Radcliffe Infirmary, Oxford, G.W. Scott Blair and myself led to an Informal Discussion, entitled "Flow Properties of Blood and Other Biological Systems", convened jointly by the Colloid and Biophysics Committee of the Faraday Society and the British Society of Rheology. It was locally promoted by R.G. Macfarlane and held at the University Laboratory of Physiology, Oxford in September 1959 [11].

The great success of the conference in Oxford in 1959 came to the attention of Robert Maxwell, publisher of Pergamon Press, who encouraged the publication of an international journal, founded by A.L. Copley and G.W. Scott Blair, and named BIORHEOLOGY - AN INTERNATIONAL JOURNAL. It began as a quarterly publication in 1962 and since 1974 is published bimonthly. In 1972, it became the official journal of the International Society of Biorheology.

In 1962, I was asked by R.S. Marvin of the National Bureau of Standards, Washington, D.C., co-chairman of the Fourth International Congress on Rheology, held in August 1963 at Brown University, Providence, R.I., U.S.A., to organize a session on biorheology. This happened just prior to a journey to Europe where I found enthusiastic support. Moreover, I was fortunate to secure financial support for more than thirty participants from many countries. Instead of one session at the Congress, as originally proposed, we had eleven sessions, comprising the Symposium on Biorheology [12] and, in addition, three lectures before the entire Congress. These presentations on hemorheology and other branches of biorheology contributed more than any previous meetings to the establishment of biorheology as an organized science. I dedicated the Symposium volume to one of its participants, my friend Robin Fåhræus as "Pioneer and Nestor of Contemporary Hemorheology".

In 1965, I thought the time was ripe to have an International Conference on Hemorheology, which I organized together with G. Bugliarello, A.C. Burton, L.E. Gelin, M. Joly, H. Hartert, S. Oka, G.W. Scott Blair, A. Silberberg, R.E. Wells and R.L. Whitmore in July 1966 at the University of Iceland under its auspices in Reykjavik. At this conference the International Society of Hemorheology was founded and I was elected its first President. A number of papers on clinical hemorheology were reported and Robin Fåhræus became the first Poiseuille Awardee of the new Society [13].

The Second International Conference of the International Society of Hemorheology, with Helmut Hartert as Chairman, took place at the University of Heidelberg under its auspices in 1969. At this conference it was decided that the International Society of Hemorheology should be extended to include all other fields of biorheology and was renamed "The International Society of Biorheology". Soon after, the Society became an Affiliated Commission of the International Union of Pure and Applied Biophysics.

The First International Congress of Biorheology was held, in association with the VI. International Congress on Rheology, at Lyon, France in 1972. Prior to the Congress at Lyon, our Society was represented at the IV. International Congress of Biophysics, held at Moscow University, USSR, with a special "Symposium on Biorheology" [23].

The Second, Third, Fourth and Fifth International Congresses of Biorheology took place in 1975 in Rehovot, Israel at the Weizmann Institute of Science; in 1978 in La Jolla at the University of California/San Diego; in 1981 in Tokyo at Jikei University; and in 1983 in Baden-Baden, F.R. Germany under the auspices of the University of Freiburg i.Br. The Sixth International Congress of Biorheology took place in 1986 in Vancouver, B.C., Canada. The Proceedings of all International Congresses of Biorheology were published in *BIORHEOLOGY*. Many communications dealt with clinical hemorheology, presented as plenary lectures, symposia, papers and exhibitions.

Clinical hemorheology is practiced more and more by many physicians, surgeons and biomedical scientists in many countries. Laboratories of biorheology including clinical hemorheology, and even departments become increasingly available in medical schools, universities, research institutions, hospitals and blood transfusion centers all over the globe.

The marked increase of original contributions to clinical hemorheology necessitated a journal of clinical investigations to serve as an aid in the practice in many fields of medicine. I founded this journal, named *CLINICAL HEMORHEOLOGY*, and asked Siegfried Witte to join me as Co-Editor-in-Chief. It began publication as a bimonthly journal in 1981. Its aims are to acquaint physicians and surgeons with clinical hemorheology and to advance hemorheological diagnostic, therapeutic and prophylactic approaches toward better medical care. Leading investigators in clinical hemorheology from many countries serve as Editors. The new journal is a Companion Journal of *BIORHEOLOGY*.

Communications dealing with clinical hemorheology are published since 1981 in **CLINICAL HEMORHEOLOGY**, while those on theoretical and experimental hemorheology appear in **BIORHEOLOGY**.

The dissemination of knowledge regarding hemorheology occurred in several ways. A number of lectures, sessions and symposia were jointly organized by the International Society of Biorheology with the International Congress of Hematology, the International Congress of the International Union of Physiological Sciences, and the International Congress of Biophysics, among others.

The advancement of clinical hemorheology was not limited to the activities of international or national biomedical societies or groups. The "United States-Japan Cooperative Seminar on Hemorheology and Thrombosis", which I initiated, was organized with Shosuke Okamoto as United States and Japan Coordinators and held at Kobe, Japan in 1975 in association with the National Science Foundation of the United States and the Japan Society for the Promotion of Science [14]. A Symposium on Biorheology, initiated by Ching-Rong Huang and organized by him and A.L. Copley, took place in New York at the annual meeting of the American Institute of Chemical Engineers in 1977 [15]. The New York Academy of Sciences held in 1982 in New York an international conference, which I initiated, entitled "Surface Phenomena in Hemorheology. Their Theoretical, Experimental and Clinical Aspects", organized by A.L. Copley and G.V.F. Seaman [16].

At the International Congress on Blood Transfusion, held in Tokyo in 1960, I was invited to give a Special Lecture on Hemorheology, co-authored by G.W. Scott Blair. This lecture stimulated research studies on hemorheology, including clinical hemorheology, in Japan and later led to the foundation of the Japan Society of Biorheology [24]. Thereafter, other national societies or groups were founded. They are the French Society of Biorheology (*Société de Biorhéologie de Langue Française*), the German Society of Clinical Hemorheology, the Italian Society of Hemorheology, the Forum of Clinical Hemorheology of the Royal Society of Medicine (England), the Portuguese Society of Hemorheology, the French Working Group on Red Blood Cell Filtration (*Groupe de Travail sur la Filtration Erythrocytaire*), and others. Some of these organizations have more than three hundred members. A recent appeal by American and Canadian biorheologists for the foundation of an American Society of Biorheology had enthusiastic response and led in April 1985 to a meeting at Anaheim, California, where a steering committee, chaired by Shu Chien, was formed for this binational society.

Of particular interest is the establishment of the European Conference on Clinical Hemorheology, first held at Nancy, France in 1979, organized by J.F. Stoltz and P. Drouin [17]. Since that time, this Conference is held every two years in different countries and, beginning with the Second Conference, its Proceedings are published in **CLINICAL HEMORHEOLOGY**. The Second Conference took place in 1981 in London, chaired by John Dormandy, under the auspices of the

Royal Society of Medicine. The Third Conference, chaired by Holger Schmid-Schönbein and H. Rieger, was held, in part together with the Fourth International Congress of Biorheology, in Baden-Baden, F.R. Germany. The Fourth Conference, chaired by Tullio Di Perri, took place in Siena, Italy in 1985, while the Fifth Conference was held in Bordeaux, France and chaired by M.R. Boisseau.

The publication of books pertaining to hemorheology and clinical hemorheology is steadily increasing and with them the awareness of the significance of what they are intended to convey.

The teaching of biorheology and of clinical hemorheology in universities, medical schools and research institutions is on the increase. Thus far, the first Chair of Biorheology was instituted in 1980 at the Weizmann Institute of Science, Rehovot, Israel and given to Alex Silberberg. It may be expected that clinical hemorheology will become an important subject in the curriculum of medical schools.

This brings me to what, I believe, will constitute an expanded scope of clinical hemorheology. From my physiological studies of bleeding and in vivo hemostasis, made about forty-five years ago, I was fully aware that the blood and the vessel wall constitute one entity. Because of this recognition I did not limit in 1951 the definition of hemorheology to the rheology of blood, but included that of the vessel wall. In 1960, I emphasized the existence of this entity, and in 1981 proposed for it the name "vessel-blood organ" [18]. This highly sophisticated organ, penetrating all other organs, contains, in both its portions, tissues of highly diverse structures with numerous functions and a great variety of constituents. The boundary of the two portions of this organ is an endo-endothelial lining [19], proposed to consist of fibrin and fibrinogenin (i.e. fibrinogen clotted without thrombin participation). Fibrin(ogenin) is considered to surround the endothelial cells and to be one of the main constituents of the basement membrane. Accordingly, fibrin(ogenin) is thought to play a crucial role in transcapillary transport [20]. Its proposed physiological presence provides a bridge between the two portions of the vessel-blood organ [25].

Recently I emphasized [1] that modern clinical hemorheology will need to be extended to include the rheology of the interstitial spaces and their contents, the parenchymal cells, the lymph channels or lymphatics, and its walls. For this extension of hemorheology I introduced the term "parahemorheology". In my appraisal, this field will play a growing role in clinical hemorheology [26].

The Editors of this book invited me to write its Introduction with emphasis on the history of clinical hemorheology as a background to the subject. Advancement of knowledge of the vessel-blood organ is expected to widen the scope of clinical hemorheology. This volume is the result of concerted great efforts by the Editors and Authors to communicate to the Readers the present status and scope of this clinical branch of the science of biorheology. The learned contributions by

the Authors of this book serve as an introduction to the expanding role of clinical hemorheology towards better medical care and the maintenance of health.

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