BIOPHYSICAL MECHANISMS IN VASCULAR HOMEOSTASIS AND INTRAVASCULAR THROMBOSIS

EDITED BY
PHILIP N. SAWYER

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INTRODUCTION BY

HAROLD A. ABRAMSON

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To
Grace
Margaret
Elizabeth
Susan and
Philip Michael
whose forbearance and patience
made this monograph possible

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PREFACE

It became apparent in the year 1963 that a considerable body of pertinent information was being obtained which served to tie together the relationship between interfacial phenomena, thrombosis, and hemostasis. Available information in this area had been acquired by a very small group of investigators who exchanged and complemented each other's findings, but did so in a very narrow spectrum without wide dissemination of their results. It seemed important that the information be called to the attention of the interested scientific public. As a beginning, a considerable effort was made to construct a symposium capable of attracting and maintaining the interest of members of such diverse specialties as vascular surgery, hematology, biophysics, and engineering.

Many of the participants of this conference have made extraordinary contributions to the knowledge of interfacial phenomena in biologic membranes, particularly with respect to blood cells and vessel interfaces. Many of the investigators had become discouraged at the lack of attention to progress in this area. Several had, indeed, given up any further effort in the belief that it was not particularly profitable to publish work in a vacuum. Some were following their scientific pursuits in a state of quasi-isolation, not realizing that others were doing work that would correlate with and augment their past and current research. The participants represented a cross-section of investigators from almost the entire spectrum of scientific and technical activity.

To the delight of the participants and the conferees, the story which unfolded during the two days of the conference created an aura of excitement and anticipation. This, on occasion, mistakenly led the participants to believe that the conference chairman was responsible for the observed results.

This conference is the first of its kind since a similar one which was held one morning as a subsection of the First International Conference on Thrombosis and Embolism in Basel, 1954. It, therefore, represents both a new starting point and a new source of information for the scientists who presented papers at the conference and the conferees.

It is impossible for the printed word to duplicate the ferment produced at such a meeting. Much of the enthusiastic discussion and querying is perforce lost in editing the conference comments. However, I tried to include as much of the information and spirit of the conference as possible.

I must acknowledge the great effort and sustained support of all who helped to organize the conference and publish this monograph: Drs. Harold A. Abramson, Walter H. Brattain, Herbert C. Lichtman, Melvin H. Kniseley, William J. Williams, and Sigmund A. Wesolowski. Dr. Clarence Dennis, Chairman of the Department of Surgery, gave me his enthusiastic encouragement at all times.

In addition, I am grateful for the help of my secretary, Mrs. Betty Novick, and the clerical assistance of Mrs. Lillian Shore; the interest and support of Dean Robert A. Moore, Dr. Joseph K. Hill, Dr. E. E. Suckling, Mr. Milton Miller, Mr. Robert Renck and his staff, Mrs. Evelyn Goodwin, Mrs. Sylvia Blin, Mr. Bruce

Burrowes, Mr. Robert Morrisson, Mrs. Charles C. Fries, and Mrs. James Murphy; the editorial efforts of Appleton-Century-Crofts and of my assistants who gave much of their time in arranging the manuscript and proofreading the galleys, Mr. Harold L. Asch and Miss Jeannette Ogoniak.

Finally, I should like to acknowledge and give thanks for the very significant contribution of the National Heart Institute of The National Institutes of Health, United States Public Health Service, through Grant HE 09 212 - 01, which made both the conference and this monograph possible.

PHILIP N. SAWYER

INTRODUCTION

Progress in medicine has forced the members of the medical profession to study more closely the mechanisms of both hemorrhage and thrombosis. Thrombosis of arteries and veins, and especially of coronary arteries, is, despite all ancillary considerations, probably the greatest cause of death of Western man today. Solution of both problems, hemorrhage and thrombosis, depends ultimately upon understanding the dynamic interactions between the walls of the vascular system and the blood flowing through that most complex system of tubes. These interrelationships maintain vascular patency and normally prevent intravascular thrombosis.

Since ancient times, the surgeon has accepted the fact that bleeding in incised tissues would eventually cease. That hemostasis is not obligatory is shown by bleeding in the hemophiliac and in other abnormal bleeding states following incision. On the other hand, it has also become increasingly evident that the natural mechanisms which preserve vascular patency deteriorate progressively with age.

Progress in gaining an understanding of the mechanisms of the interactions between blood vessel wall and the components of the blood was prevented by a number of factors. The first of these was the early need to control acute causes of death. Paradoxically, the second was inherent in our education, which until recently prevented the use of information and techniques from other scientific areas to solve essentially biologic problems. The third was the fact that the techniques of enzyme chemistry proved so effective in studying blood clotting, that for years virtually all study and interest were centered in this area.

That surface chemistry is involved in blood clotting has become increasingly evident in the twentieth century. For example, blood exposed to gaseous interfaces and glass surfaces clotted; placed in glass properly coated with any one of a number of surface active agents, including silicone, paraffin, and negatively charged plastic surfaces, blood could be kept liquid for more extended periods of time. Techniques for keeping blood liquid were eagerly used by hematologists to study blood clotting per se, but the causal relationship between charged surfaces and vascular thrombosis was not fully appreciated. Thus, for eighty years, since the classical studies of Bizozerro and Zahn, almost no additional information was produced concerning the interreaction between vessel wall and contained blood which resulted in intravascular thrombosis. The few attempts made to study the problem of vascular homeostasis were consistently greeted with failure. But clinical implications of both phlebitis and atherosclerosis indicating the critical interreactions between the vascular tree and blood became increasingly obvious.

Finally, in 1927, it was unequivocally demonstrated that all blood cells were negatively charged at the pH of the blood and moved towards the positive pole in an electrophoretic cell. Though this information excited physiologic interest, it caused little clinical comment, even though the probable significance of these phenomena in relation to intravascular thrombosis was emphasized. After an additional lag phase of twenty years it was found that small electric fields, applied in vivo to the aorta and vena cava, would both cause and prevent intravascular thrombosis.

Simultaneously, large changes in the potential difference across blood vessel walls were found concomitant with thrombosis. Application at the clinical level resulted in the development of direct current coagulation in which a positively polarized electrode was used to hasten hemostasis. During the past ten years, related aspects of the problem have been investigated including the effects of electric currents and surface charge on everything from prevention of thrombosis of small vessel anastomosis to application of currents to speed wound healing.

It appeared that new discoveries in this area were being made at an increasing rate and that the information deserved wider dissemination than was available among the small group of people actively working in different areas in the field. Therefore, this conference was organized to indicate at a basic level the relationships of electrokinetic and other interfacial phenomena to the biological questions touched upon in the foregoing. Session 1 was entitled "Fundamental Electrokinetic Phenomena" and was chaired by Walter H. Brattain, co-discoverer of the transistor. The papers presented at this meeting illustrate the significance of interfacial phenomena of blood cells, tissue surfaces, and blood vessels in their physiological environment. This section illustrated the effectiveness of application of simple techniques in physics to the solution of biological problems which have long defied quantitative evaluation.

In Sessions 2A and 2B, more detailed application of various electrokinetic and interfacial phenomena, to both blood cell and the vascular tree, was expounded. Drs. Harold A. Abramson and Torsten Teorell were co-chairmen and presided over talks delivered by investigators concerned with the significance of physical phenomena to vascular homeostasis and thrombosis. Following intermission, a panel discussion was held which included all of the early participants. They discussed the electrochemistry of the vascular interface, the prevention of mural thrombi, and the rheology of blood. Walter H. Brattain again moderated. A bit of the contagious enthusiasm of the panel can be found in the transcript of the discussion.

A logical extension of the first day's presentations involved a study of the actual effects of electricity on the production of blood clotting in vivo and in vitro. Session 3 was chaired by Drs. Melvin H. Knisely and Walter H. Seegers. Contributions of platelets and of other materials to blood clotting per se, and the possible relationship of interfacial phenomena to the prevention of adherence of the blood particles, were discussed in this part of the meeting. Next, biochemical and biophysical mechanisms by which interfacial phenomena at the intimal surface of blood vessels may be mediated and modified were presented. These included various aspects of the physical structure of the vascular membrane and its interaction with blood flowing through the vessel.

In Session 4, co-chaired by Drs. Sigmund A. Wesolowski and Philip J. Boddy, the practical aspects of the construction of more suitable vascular prosthesis, as deduced from recent contributions to the knowledge of the vascular interface, were discussed. In the last discussion, moderated by Dr. Philip N. Sawyer, scientists representing physics, biochemistry, pathology, hematology, and physiology endeavored to determine where the current investigations are headed by determining where we have come from and where we are now.

The implications of this meeting in terms of modifying abnormal physical, chemical, and biochemical phenomena which produce intravascular thrombosis suggest several practical approaches to the construction of more satisfactory prostheses whose function depends on the maintenance of patency and prevention of mural thrombus formation.

The possibilities of modifying available biological membranes so that they lose tissue specificity while they maintain their resistance to thrombosis, and the implications of interfacial phenomena as a measure of antigenic behavior, are all suggested outgrowths and logical extensions of this conference. Here a fruitful interchange was achieved. Its significance to the future knowledge of the vascular tree and to the future of vascular surgery suggests that we may expect even more important contributions in the near future. The ultimate hope is that the conference will act as a catalyst in the study of abnormal metabolism productive of intravascular thrombosis. Examination of the information recently made available suggests that this problem may soon be resolved.

HAROLD A. ABRAMSON

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CONTENTS

Session 1: FUNDAMENTAL ELECTROKINETIC PHENOMENA

Chairman: WALTER H. BRATTAIN

Dr. Clarence Dennis: Welcome on behalf of the Department of Surgery. Dr. Sawyer points out that a lot of work has been done in vitro, but not much has been done in vivo. An immense amount of work has been done on classical metabolism and what this may be doing to thrombosis of the important vessels.

There is another group which has spent a good deal of time and thought on rheology, even though there is little quantitation, and there is a group headed by Dr. Sawyer which is studying the bioelectric factors involved in thrombosis and maintenance of the fluid state of the blood. This group has been working over a period of more than a decade.

With all of these groups working in the area of blood clotting and intravascular thrombosis, it seemed as though there should be some medium by which they could exchange their ideas. It was Dr. Sawyer's idea that this conference could serve this purpose.

Without further ado, I will introduce the Dean of our Medical School, Dr. Robert A. Moore, who has been professor of pathology at another medical school and has been dean at two other medical schools in addition to this one.

When he elected to come to the State University, I for one changed my mind about leaving. I am delighted that I stayed. I trust he will tell you a little about what he has been able to accomplish while he has been here.

Dr. Robert A. Moore: Thank you, Dr. Dennis. On behalf of the Downstate Medical Center of the State University of the State of New York, I want to welcome you here.

The State University of New York differs from most universities in this country in that, first, it is located in fifty-eight different places in the state. It is a decentralized university. We have no single campus which we call the university.

There is a group of officers in Albany with a president and comptroller, business manager and attorney having their offices there, but there is no central campus.

Downstate Medical Center is one of the fifty-eight centers, units so-called, in the university, and one of three medical schools within the University System. The other two are at Syracuse and at Buffalo.

I am sorry that you didn't come here just about a year from now when you might go through and work in the new building behind this medical school building, the new University Hospital, a 350 bed hospital with an out-patient department and a clinical science building controlled by the clinical departments where there will be offices and research space.

The two large buildings you see directly behind this end of the medical school are the two new residence halls of the Downstate Medical Center. The two together will hold about 550 beds. We call it beds rather than students because seven-ninths of that building consists of one- and two-room apartments for married students. Two floors in this building are devoted to dormitory rooms in the usual sense.

I would like to say just a word about your program. As I looked at it and Dr. Sawyer asked me to come here this morning, my mind went back about thirty years when Dr. Gardner Childs and I, at the New York Hospital, were working on prothrombin and Vitamin K.