# BLOOD CELLS

EDITED BY JAMES L. TULLIS

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# BLOOD CELLS and PLASMA PROTEINS

## *Their State in Nature*

**Edited by James L. Tullis**

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The *Memoirs of the University Laboratory of Physical Chemistry Related to Medicine and Public Health, Harvard University*, metamorphose after a period of pupation from the series of seminars held each winter in Harvard Hall in a field chosen because it appears to be approaching that critical moment in time when,

"Where New apperance is before the Eyes,
New Suppositions thereupon arise."

The subject of the seminars and the experts, often representing different disciplines, who are invited to participate, are selected with the intent to "cross the conventional boundaries of the specialties . . . on the frontiers of knowledge" the function of a University Professor at Harvard.

Following each seminar, the Editor chosen for the series brings to the attention of each expert the thinking of his fellow participant in the seminars, in the hope that this cross fertilization may stimulate new advances and in the expectation that each chapter of the *Memoirs* may be revised until it is published. The *Memoirs* thus are intended to reflect the thinking of the contributing experts, not at the time of the seminar, but at the time that the corrected manuscripts are completed.

One result has been the inevitable influence of each series of seminars upon the next; a natural outgrowth which was not foreseen, but which will readily be recognized in retrospect.

E. J. C.

# PREFACE

In 1921 Fahraeus undertook a study of blood sedimentation. In the course of his work an attempt was made to trace the history of the earliest observations on the settling of blood. Fahraeus was surprised to find that, like many observations on natural events, early knowledge extended back to the time of Hippocrates. Moreover, this simple biologic phenomenon was in large part responsible for the entire Greek concept of health and disease: the presence of four body humors—dark bile, light bile, phlegm, and blood. Greek observers correctly noted that blood from a healthy person clotted and that this clot expressed a second humor; clear bile. Blood from a diseased person, however, expressed two extra humors; dark bile (the packed red cells at the bottom) and phlegm (the leucocytes on top). The division of a clot into these two extra humors was, of course, a reflection of the accelerated sedimentation of diseased blood permitting time for separation of a buffy coat before clotting was complete. The "phlegm" was not necessarily increased in disease, as the Greeks had presumed, but merely more readily seen. Fahraeus states:

> "One wonders how it was possible that a philosophical system, so faulty at bottom, could send forth such a vigorous shoot into a practical discipline such as medical science is, and which, even at the time of its most primitive practice, had, to some degree, to be founded on observations from nature. The explanation of this is that the theory came very near reality."

In similar fashion, many of the apparently divergent facts in modern knowledge about blood are beginning to fit into a logical pattern. Re-examination of recent advances reveals that conflicts only appeared to exist. The observations generally were correct. The conclusions occasionally were wrong. Early in the twentieth century, the Italian schools recommended the use of blood transfusions for the treatment of thrombocytopenic purpura. Lacking suitable anticoagulants, the blood was given by

direct transfusions through paraffin-coated syringes. With the introduction of citrate by Lewisohn in 1908, however, it became possible to store blood in glass bottles for subsequent indirect transfusions. During succeeding decades, data were brought forward to show that blood transfusion often was not helpful in thrombocytopenic purpura. We know now that the original observation was entirely correct. The introduction of citrate had simply halted the use of blood in its natural state. It was no longer collected in paraffin, but through rubber into glass, both wettable surfaces, completely foreign to blood. The platelets for the most part were destroyed.

This volume, Number 2 in the series of *Memoirs of the University Laboratory of Physical Chemistry Related to Medicine and Public Health*, deals with the present state of knowledge about blood and its component parts. The original thinking was largely crystallized through a series of seminars delivered at Harvard Hall, Cambridge, Massachusetts, during February, March, and April of 1951.

The manuscripts of the various contributors have been grouped into seven general categories. Following Provost Paul H. Buck's opening remarks, delivered at the beginning of the seminar series, there is a section consisting of four chapters by Dr. Edwin J. Cohn. The first of these chapters presents an historical review of the development of knowledge about blood, beginning in Padua during the sixteenth century and continuing through to the discovery of the elementary composition of plasma proteins during the nineteenth century. In the second chapter, the plasma proteins are classified in terms of their interactions with neutral salts and their solubility in ethanol-water mixtures at low temperatures. Chapters 3 and 4 present the recent characterization of proteins by virtue of their interactions with each other, with heavy metals, with specific polysaccharides and with blood cells. This includes a new method of protein fractionation based on specific protein-metal interactions at neutral pH. Evidence is presented regarding the fine structure of serum albumins on the basis of their amino acid composition and the disassociation of free groups. This fundamental concept of protein fine structure will be developed more fully in a subsequent volume by Dr. Cohn.

In Section II, the complex factors concerned with blood coagulation are discussed in a series of five chapters by different

authors. Dr. Surgenor presents evidence concerning the chemical nature of prothrombin and certain of the accelerator substances. Dr. Alexander gives particular attention to the role of the accelerator substances in hemostasis. Dr. Ferguson presents fundamental observations on the functions of the various clotting factors in isolated systems of purified reagents. The chapter by Dr. Edsall deals with basic observations on the interactions between thrombin and fibrinogen. The last chapter of this section presents new data on the role of blood platelets in the coagulation mechanism as well as techniques for the long-term preservation of these cells.

The characterization of immune antibodies is given decisive treatment in Section III. In the opening chapter, Dr. Janeway discusses the role of each component of blood concerned with immunity. In a succeeding chapter, Dr. Enders points out the significance of gamma globulin fractions prepared from pools collected in various geographical areas. The physical characteristics of the globulins are delineated in a chapter by Dr. Oncley. A final chapter by Dr. Ehrich presents evidence regarding the plasma cell source of immune antibodies. Unfortunately, the lecture on characterization of the four components of complement presented by Dr. Michael Heidelberger at the original seminar series could not be included in this volume.

The section on erythrocytes opens with a general review by Dr. John Gibson. This is followed by two chapters on the problems of red cell preservation by Dr. Strumia and Dr. Pennell. A final chapter by Dr. Orville Denstedt presents new and stimulating data on the enzymology of the erythrocyte. The concepts developed therein present a challenge to workers in the field of red cell preservation.

The section on leucocytes begins with the development of knowledge about white cells and presents experience with their separation and preservation. A succeeding chapter by Drs. Claude-Starr Wright and Doan raises new concepts concerning the role of white cells in bodily defense. Problems dealing with histamine content of white cells are brought forward in a chapter by Dr. Code. In the final chapter of the section, Dr. Britton Chance presents data obtained from the application of new spectrophotometric measurements to cytochrome components of leucocytes and other types of cells.

The section on plasma enzymes, by Drs. Surgenor, Hunter,

and Brown of this laboratory, needs no amplification here. It is fully discussed by Dr. Joseph Fruton.

The final section dealing with lipoproteins has been considerably extended since the original seminar series. Following the opening chapter on the properties of lipoproteins, and a succeeding chapter on lipoprotein characteristics as defined by study of brain tissue, three new contributions have been added. Dr. Michel Macheboeuf of the Pasteur Institute has contributed a chapter on various physical characteristics of the lipoproteins of plasma and serum. Two succeeding chapters by Dr. Barr and coworkers at Cornell University and Dr. Lever of this University present interesting new data regarding lipoprotein partition in various disease states related to atherosclerosis and diseases of abnormal lipid metabolism.

A chapter by Dr. George Scatchard and coworkers on The Interactions of Proteins with Small Molecules and Ions has been reluctantly withheld for inclusion in a subsequent volume, Memoirs 3, Specificity in Biologic Interactions.

The original seminar series was appropriately complemented by two concurrent exhibits. The first, a display of nineteenth and twentieth century equipment for use in blood transfusion and blood study, was held in the Holden Chapel of Harvard University and was in large part organized through the cooperation and effort of Dr. Charles C. Lund, of Boston. The second, a collection of early manuscripts on The History of Knowledge about Blood, was organized by Professor I. Bernard Cohen and displayed in the Widener Library of Harvard University. A catalog of this collection, assembled by two of Professor Cohen's graduate students, Messrs. Duane H. D. Roller and Wyndham Miles, has been published separately by this Laboratory.

James L. Tullis

*University Laboratory of Physical Chemistry*
*Related to Medicine and Public Health*

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# INTRODUCTORY REMARKS

PAUL H. BUCK

It is a pleasure, on behalf of Harvard University, to open the second series of theoretical seminars held by the University Laboratory of Physical Chemistry Related to Medicine and Public Health. The seminars themselves, on *Blood Cells and Plasma Proteins: Their State in Nature*, are peculiarly apt in their dissemination of fundamental knowledge vital in the period of world history in which we find ourselves. Their location in Harvard Yard marks a spiritual joining of the work of the University Laboratory with that of its Cambridge collaborators in chemistry and physics which has proved so fruitful in the development of knowledge of significance in the fields of public health and human therapy.

The choice of Harvard Hall as the site for these seminars is a singularly happy one, for Harvard Hall may be regarded as the center from which were disseminated the natural sciences in the University and throughout the nation in its early days. The original Harvard Hall, "New College," was built in 1677. Far more important than its position as the "focal point for a reorientation of the college buildings into the open quadrangle shown on the well-known 'Prospect of the Colleges in Cambridge'" (1776), noted by Samuel Eliot Morison, was its development into a focal point in the introduction to America of the "New Science" of Galileo, Boyle, Harvey, Borelli, Wren, Lower, and the other great men of the age just before Newton. Harvard Hall was nine years old when, on the invitation of Samuel Nowell and Increase Mather, Charles Morton came from England to accept the call to the pastorate of the First Church in Charlestown and delivered the first general lectures in "Natural Philosophy" for the students of the University. Morton's *Compendium Physicae*, copied by generations of Harvard students, has been described as the major vehicle by which the "New Science" was introduced into the New World. Morton provided students with a broad survey of all the major branches of science, including physics, chemistry, meteorology, astronomy, geology and mineralogy, biology, and physiology. The blood, in

terms of its circulation, physics, chemistry, and physiological functions, was given a prominent place.

The original Harvard Hall was destroyed by fire in 1764. On its site rose the present building, with its "Musaeum" and with the first rooms at Harvard designed especially for lectures and recitations. Later, it housed the country's first experimental physics laboratory, where apparatus procured by Benjamin Franklin was used in the physics and natural philosophy courses conducted by John Winthrop. Here also were held "some medical and chemical lectures," subsequent to which the Harvard Medical School was established in 1783 in neighboring Holden Chapel. Harvard Hall may thus be considered the point of germination of the scientific and philosophical ideas which first made Harvard a University. Benjamin Waterhouse, first Hersey Professor of the Theory and Practice of Physics in the Medical School, returned to the Philosophy Chamber of Harvard Hall to house his natural science collections, and he there gave the first lectures on natural history in the University.

It is perhaps a century since scientific lectures have been delivered in this historic building, and it is appropriate that the seminars of the University Laboratory of Physical Chemistry Related to Medicine and Public Health should be held beneath this roof. The close relationship with Holden Chapel in the early period of scientific and medical development was recently fittingly signalized under the sponsorship of the University Laboratory by an exhibition there of equipment for the collection, processing and transfusion of blood, from the nineteenth century to the present time, which is intended to supplement and to extend the period represented by the collection of manuscripts and books on the Development of Knowledge of Blood, from 1490 to the nineteenth century, assembled for exhibition in Widener Library.

PAUL H. BUCK

*Provost of the University*

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