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Red Cell Metabolism and Function

Edited by George J. Brewer

Red Cell Metabolism and Function

Proceedings of the First International Conference on Red Cell Metabolism and Function, held at the University of Michigan, Ann Arbor, October 1-3, 1969

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PREFACE

In the last six years, a remarkable series of studies have demonstrated an intimate relationship between red cell metabolism and the function of the cell as an organ of gas transport. First came the demonstration of binding of organic phosphocompounds of the red cell to hemoglobin; this was followed by studies that demonstrated modification of hemoglobin oxygen affinity by such binding. At present we are in an exhilirating phase of accrual of data showing that the levels of these phosphorylated intermediates can be rapidly altered in the red cell to modulate hemoglobin function. At one time it was said that the red cell was an inert bag full of hemoglobin. Now we know not only that the cell has an active metabolism crucial to its viability, but that this metabolism is just as crucial to the whole organism in the proper adjustment of oxygen transport.

On October first, second and third, 1969, red cell biochemists, general biochemists, geneticists, cardio-pulmonary physiologists, exercise physiologists, experts in blood storage, and representatives from many other disciplines met in the Towsley Center for Continuing Medical Education at the University of Michigan, Ann Arbor, to present recent findings and discuss developments in this new interdisciplinary field. The meeting was dedicated to Dr. Alfred Chanutin, Professor Emeritus of the University of Virginia, to honor his retirement in 1967 and in recognition of his great contributions to the studies outlined in the first paragraph of this preface.

The program dealt with our present understanding of binding of organic phosphocompounds, and certain other substances, to hemoglobin, and how the binding affects oxygen dissociation properties. Interaction with the acid-base status of the blood was emphasized, as was interaction with carboxyhemoglobin, particularly in smokers. Changes in levels of phosphorylated intermediates in several hypoxic conditions, and the resulting effect on oxygen dissociation, were reported. Metabolic control mechanisms in the red cell and mechanisms of pulmonary and systemic gas transport were discussed at length. The effect of exercise on gas transport and red cell intermediates, and comparative aspects of gas transport were considered. An entire session was devoted to the serious problem of the capability of stored blood to transport oxygen after transfusion, particularly after the first 1-2 weeks of storage, in view of the marked decline of organic phosphocompounds during storage.

This volume, the Proceedings of the above Conference, represents a comprehensive coverage of these new and important developments. The major part of the volume is comprised of the formal manuscripts, which present a rich bounty of new data and formulations. At the end is appended the recorded discussions of the papers, in sequence according to the order of the presentations. In toto, the volume displays the interchange of current thinking

on the problems of oxygen transport in health and disease.

The Editor would like to acknowledge the invaluable assistance of Mrs. Lynne Bowbeer in the organization of the Conference, assistance with the Conference, and in compilation of this volume. I am very grateful to Dr. John W. Eaton for generously given advice and assistance. I also thank Colonel Lawrence Rose, Dr. and Mrs. John Faulkner, Miss Lucia Feitler, Mr. David Bowbeer, Mr. Conrad Knutsen, Mr. Dinu Patel, Miss Kathleen Hilden, Mrs. Eleanor Miller, Dr. C.J.D. Zarafonetis, Dr. James Neel, Mr. Robert Richards, Mrs. Katherine French, and Dean William Hubbard, Jr. for their help and support. Financial support from the US Army Medical Research and Development Command and Abbott Laboratories made the Conference possible. The staff of Plenum Press has been most patient and helpful.

THE EDITOR

October 17, 1969

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DEDICATION

OF THE FIRST INTERNATIONAL CONFERENCE ON RED CELL METABOLISM AND FUNCTION TO

DR. ALFRED CHANUTIN

UNIVERSITY OF VIRGINIA

It's a great pleasure for me to dedicate this meeting and the Proceedings which will subsequently be published to Dr. Alfred Chanutin, Professor Emeritus of Biochemistry, University of Virginia.

Dr. Chanutin was born June 3, 1897 in New Haven, Connecticut. He received his Ph.B. from Sheffield Scientific School, Yale University in 1917. He was an Assistant in the Dept. of Medicine at the University of Pennsylvania in 1919, an Assistant in the Dept. of Physiology at Cornell Medical School in 1920, and obtained his Ph.D. from Yale in 1923. He was an Instructor in Physiology at the University of Illinois for a year and then accepted a position as Associate Professor of Biochemistry at the University of Virginia in 1924. He has been at Virginia since that time. Dr. Chanutin was promoted to Professor of Biochemistry, and became the first Chairman of the Department of Biochemistry at Virginia, in 1929. He retired in 1967 after serving a record term at Virginia of 38 years as a full professor.

Dr. Chanutin is a member of the Society for Experimental Biology and Medicine, the Southern Society of Clinical Investigation, the Radiation Research Society, the American Society of Biological Chemistry, the American Chemistry Society, Alpha Omega Alpha, and Sigma Xi. He has been a member of the Hematology Study Section of the National Institutes of Health, and the Subcommittee on Sterilization of Blood and Plasma of the National Research Council. He has served as a Consultant to the Research and Development Command, Office of the Surgeon General, to the Medical Division of the Chemical Corps and to other groups too numerous to mention.

Aside from his work on red cell biochemistry to which we will turn in a moment, he is widely known for studies on creatine metabolism, the biochemistry of renal insufficiency produced by partial nephrectomy, the biochemical effects of chemical warfare agents, trauma, thermal injury and Xray-irradiation, studies on fractionation and electrophoresis of plasma proteins, and studies on protein-calcium interaction.

But it is for his work in the field of red cell biochemistry that we particularly wish to honor him here today. Glancing over Dr. Chanutin's bibliography, there are some 2 dozen publications on the red cell, mostly in the last dozen years. His interests in the red cell, like his interests in general, are wide ranging.

His papers include work on preservation of human red cells, metabolism of human red cells in health and disease, and electrophoresis of hemolysates of fresh and stored cells. In a series of papers beginning in 1957, Dr. Chanutin and his co-workers began to note differences in hemoglobin electrophoretic patterns according to the condition of the blood e.g. the patterns were different after the blood had been stored for long periods. In 1963 Sugita and Chanutin suggested that the alterations in electrophoretic patterns could be explained by the formation of a complex between hemoglobin and phosphoric acid esters, such as 2,3-diphosphoglycerate (DPG) and adenosine triphosphate (ATP), the two phosphorylated intermediates present in largest amounts in the human red cell. They demonstrated that incubation of stored hemolysates with DPG and ATP would regenerate the original electrophoretic patterns. These effects were further elucidated and expanded in papers in 1964 and 1965. This series of observations led Dr. Chanutin to study the effects of these same phosphorylated intermediates on the oxygen dissociation properties of hemoglobin, with the results published in a landmark paper in 1967 (Chanutin and Curnish, 1967) entitled "Effect of Organic and Inorganic Phosphates on the Oxygen Equilibrium of Human Erythrocytes." Of course, we all know the significance of these observations. It is possibly an acceptable view that publications beginning in 1967 from other laboratories featuring the effects of phosphorylated intermediates on hemoglobin oxygen dissociation properties were also stimulated by the early Chanutin papers on the binding effects between phosphorylated intermediates and hemoglobin.

The papers submitted to this conference stand in testimony to the importance of this area of study initiated in large part by Dr. Chanutin. The story has unfolded in truly dramatic fashion as we find that changes in levels of intermediates such as DPG can explain long-puzzling and important phenomena such as the differences in the oxygen dissociation curve between hemoglobin and intact cells, and the right-shifted oxygen dissociation curve of high altitude anemia, pulmonary disease, and of exercise. The interdisciplinary nature of this conference demonstrates how widespread the ramifications of this area have become. It is obvious that the pulmonary physiologist, the exercise physiologist, the hematologist, those interested in biochemical control mechanisms, and those interested in blood storage, as well as other disciplines, must take note of the red cell findings if they are to understand oxygen transport.

Now if I may interject a personal note. In organizing this conference, Dr. Chanutin's advice and help have been invaluable. And as I talked to people around the country, I became aware that he had been just as helpful over the years to other people. This man is beloved at his home University of Virginia and by colleagues across this country, as well as overseas.

Dr. Chanutin, it is our pleasure to honor you with this meeting, with these contributions, and with the published volume which will result from this conference.

George J. Brewer, M.D.
Conference Chairman

TABLE OF CONTENTS

IV. ERYTHROCYTE FUNCTION AFTER BLOOD STORAGE

Session 5 - G. Bartlett, Chairman

I

RELATIONSHIP BETWEEN RED CELL METABOLISM AND FUNCTION

SESSION 1 - A. Chanutin, Chairman

SESSION 2 - C.-H. deVerdier, Chairman