
The Plasma Proteins

Clinical Significance

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TO MY WIFE AND CHILDREN

FOREWORD

The advances in human knowledge have been the reward of adventurous dreamers. They saw the challenges and tilted not at windmills but at what they believed to be the ultimate and attainable goal. Undoubtedly, Leonardo would have enabled man to fly if only he had the internal combustion engine. Without it he failed! Columbus discovered the western hemisphere by good luck and a stout heart—but to both the challenge was there! From the mountain top others have seen the far vistas of new discoveries which have challenged generations of dreamers to pursue the explorations over mountains of thought as well as in valleys, only to find the end is not yet.

Since the earliest time of history it has been man's ambition to transfer blood from animal to man or from man to man. But for reasons then unknown the results were almost always disastrous. The principal reason for this was discovered in 1901 by Landsteiner. He showed that the red cells of a donor might be clumped by the plasma of the recipient or vice versa. From this discovery, it became possible to divide blood samples into different groups based on the reactions between red cells and plasma.

The study of the plasma and its contained proteins has intrigued many investigators of varied interests and diverse disciplines for the past two generations. Bayliss and Cannon in World War I formulated the theory that traumatic shock was due to the loss of plasma from damaged blood vessels. The separation of the plasma proteins into albumin, the globulins and

fibrinogen by electrophoresis which was introduced into clinical medicine by Tiselius, and their fractionation by methods developed by Cohn and his associates opened up immense new territories which are constantly being explored and yielding great riches.

It was during the early days of World War II that Dr. Weil became interested in the plasma proteins and their role in shock. He was a member of the team of investigators working with me at McGill University and the Royal Victoria Hospital, and he was among the first to show clinically the importance of the plasma proteins in burn shock and that of hemorrhage in surgical shock. Shock and transfusion remain one of Dr. Weil's major interests; he has continued to make contributions to the subject; and now he presents an up-to-date account of the broader aspects of this fascinating field of medicine.

The clinical application of the knowledge has prompted Dr. Weil to condense and place before the reader, whether mature clinician or medical student, the gist of this knowledge and its application. However, the end is not yet. Knowledge breeds curiosity, and curiosity leads to further exploration. But from time to time it is well to pause and resurvey the country over which we have traveled. There we may find other hills to explore beyond which other horizons may be discovered. In many instances, Dr. Weil has suggested such. The seeking of knowledge is not always a straight and narrow path but may have detours which can be seen best in retrospect. The search for the ultimate in plasma proteins is one such. It is for the adventurous dreamers to heed these beckonings. May they always be with us and never be discouraged!

Montreal, 1958

JONATHAN MEAKINS

PREFACE

✓ **T**HE plasma proteins are important for the regulation of many physiologic processes. The role of albumin in maintaining the normal distribution of fluid and electrolytes between blood and tissues, that of fibrinogen in the coagulation mechanism and that of gamma globulin in immunity and resistance to infection are well known.

However, other proteins of the plasma discovered or isolated more recently are of interest and importance. Although not so well known, they deserve discussion in any presentation of the subject.

The subject of the plasma proteins considered as a whole is so broad and the reports of recent investigations are so numerous that it is difficult to obtain a general view of the entire field or to find a comprehensive account of the clinical significance of the plasma proteins. To do so it is necessary to consult many different journals and textbooks. The review articles which appear from time to time are primarily designed for those interested in special aspects of the subject and therefore are restricted in scope and limited in their coverage of the plasma proteins.

Since there has not been a recent review of a general nature which deals with the plasma proteins from the clinical point of view, it was considered worthwhile to bring together in monograph form as many of the facts as possible pertaining to them. The information has been collected from the recent as well

as the older literature, interpreted in the terms of the original investigator and integrated into a form which presents the plasma proteins in their entirety.

To present the subject in this manner, with constant emphasis on the relationship of the plasma proteins—both classic and of more recent discovery or interest—to health and disease, has been the author's aim. For various reasons, including the scope of the subject and the size of the monograph, it was considered neither necessary nor desirable to attempt to cite references except in isolated instances. The references included are chosen mainly because they are reviews of a particular part of the subject or are articles which deal with fundamental aspects of it.

Another and important reason for a presentation of the clinical significance of the plasma proteins is the increasing importance of the concept of hypersensitivity in an ever-expanding area of internal medicine. Diseases affecting every organ system of the body may have as a prominent laboratory feature an alteration of the plasma proteins which may help in their diagnosis. Of equal importance, the elucidation of their pathogenesis at the present time is largely based on a theory and tested by procedures which involve the plasma globulins. For these reasons the recognition of such diseases, an understanding of their possible etiology and the knowledge of available treatment should become the property of all physicians.

The material has been prepared and published with the view that such a presentation would be of value chiefly to physicians, interns and students. If it is also of use to those with a special interest in one or more of the many aspects of plasma proteins, it will have doubly served the author's purpose.

I am greatly indebted to Mary Rosamond Weil, my wife, for her constant encouragement; to Miss Ruth E. Baldry, B.Sc., B.Sc. Pharmacy, of the Transfusion Service, Royal Victoria Hospital, for her untiring efforts throughout all stages of its preparation and in the final completion of the manuscript; to Mrs. F. D. Peart, Librarian, Royal Victoria Hospital Medical Library, for the compilation of the references.

Also, I should like to acknowledge my appreciation to Dr. J. C. Meakins, Professor-Emeritus of Medicine, McGill University, and Dr. A. H. Neufeld, Director of Biochemistry, Queen Mary Veterans Hospital, Montreal, for their kindness in reviewing the manuscript and making suggestions for the preparation of the book in its final form.

PAUL G. WEIL, M.D.

CONTENTS

1. INTRODUCTION	1
Origin of Life from Protein Synthesis	2
Precellular Formation of Protein	2
Interaction of Humoral and Cellular Factors in Blood	3
2. METHODS	5
Biochemical	5
Electrophoretic Method	5
Ultracentrifugal Method	6
Physicochemical Method	7
Combined Method	7
Immunologic Methods	8
3. ALBUMIN	11
Albumin: Origin	11
Functions	12
Hypoalbuminemia	14
Edema Due to Hypoalbuminemia	21
Therapy	22
4. PLASMA PROTEIN "SUBSTITUTES"	25
Substances Used in Treatment of Shock ..	25
Properties and Uses	26
Protein Hydrolysates	29
5. FIBRINOGEN	30
Origin and Function	30
ESR Test	30
Hypofibrinogenemic Hemorrhage	31
Treatment with Fibrinogen	32

5. FIBRINOGEN (<i>Continued</i>)	
Fibrinoid Lesions	33
Plasminogen	34
Therapeutic Possibilities of Plasmin	35
6. GLOBULINS	37
Hyperglobulinemia	38
Diagnostic Significance	38
Serum Protein Changes in Collagen Dis-	
eases	40
Multiple Myeloma	41
7. GLOBULINS (<i>Continued</i>)	44
Sarcoidosis	44
Sjogren's and Mikulicz's Diseases	45
Cystic Fibrosis of Pancreas	46
Hashimoto's Disease	46
Pathogenetic Interrelationships	47
8. GLOBULINS (<i>Continued</i>)	49
Dystrophia Myotonica	49
Diabetes	50
Pulmonary Tuberculosis	51
Hamman-Rich Syndrome	52
Berylliosis	52
Neoplasia	53
Cancer Detecting Tests	53
9. GLOBULINS (<i>Continued</i>)	56
Purpura Hyperglobulinemia and Macro-	
globulinemia	56
Dysproteinemia	56
Cryoglobulinemia	58
Macromolecular Syndrome	59

10. LIVER DISEASE	62
Hepatic Origin of Globulins	62
Changes in Liver Disease	63
Liver Function Tests	63
Diagnosis of Liver Disease	64
Therapeutic Aspects	65
11. PREGNANCY, INFANCY AND THE AGED	66
Plasma Proteins in Pregnancy	66
Gamma Globulin Level in the Newborn ..	67
Serium Proteins in the Aged	68
12. ALPHA GLOBULINS	69
Glycoproteins Vs. Mucoproteins	69
Alpha Globulins	70
Acute Phase Reactants	70
C-Reactive Protein, Occurrence and Signifi- cance	70
13. PLASMA VS. CONNECTIVE TISSUE PROTEINS ...	74
Pathogenetic Interrelationships	74
Autoimmune Theory of Disease	75
Glycoproteins Vs. Mucopolysaccharides ..	77
Rheumatoid Serum Agglutination Test ..	78
14. BETA GLOBULINS	80
Role of Lipoproteins in Atherosclerosis ...	81
Role of Lipoproteins in Xanthomatosis ...	82
15. GAMMA GLOBULINS	83
Agammaglobulinemia	84
Origin of Gamma Globulin	86
Humoral Vs. Cellular Immunity	87
Therapeutic Aspects	89

xvi Contents

16. IMMUNITY	94
Complement	94
Properdin	95
17. HEMORRHAGIC DISORDERS	98
Dysproteinemia and Purpura	98
Antihemophilic Globulin	99
Transfusion Treatment	99
Plasma Proteins and Coagulation	100
18. AMYLOIDOSIS	104
Occurrence of Amyloid	104
Primary and Secondary Forms	104
Experimental Production	105
Composition	105
Pathogenesis	106
Treatment	106
19. PLASMA PROTEIN COMPLEXES	107
Iron Proteins	107
Role in Homeostasis	108
Hemochromatosis	108
Copper Protein	110
Protein-Bound Iodine	112
20. MISCELLANEOUS PROTEINS	114
Erythropoietin	114
Hypertensinogen	114
Proteins not Normally Present in Plasma ..	115
Proteins of Other Body Fluids	117
21. CONCLUSION	119
BIBLIOGRAPHY	123
INDEX	127

1

INTRODUCTION

Within the past two decades the fluid element of the blood has assumed a clinical significance which formerly was accorded only to its formed elements, the erythrocytes, the leukocytes and the platelets. A study of the plasma proteins and their alteration in disease encompasses a large area of clinical medicine, and within the last few years a tremendous amount of investigation has been carried out in this field.

The increasing interest in the plasma proteins, especially the globulin fraction, derives from several different sources. Among them may be mentioned the development of the various methods and technics for the immunologic, electrophoretic, physicochemical or mechanical separation of the protein fractions; the vast amount of investigation in the collagen group of diseases in which the proteins are altered; the introduction of ACTH and cortisone and their influence on hypersensitivity states and diseases in which there is either hyperglobulinemia or a qualitative alteration in the globulin fraction of the plasma proteins.

Although the globulin portion of the plasma protein has obtained the major share of interest in recent years for reasons, some of which have been mentioned, the other principal fractions—albumin and fibrinogen—have not been neglected. The availability of albumin, antihemophilic globulin, fibrinogen and gamma

2 Introduction

globulin in purified form for human use has been a major therapeutic achievement. The fractionation and the availability of other protein substances, *e.g.*, properdin for the treatment of infection, and plasmin from its precursor plasminogen for the therapy of thrombosis are examples of the more recently discovered proteins which may be expected to advance medical science as further findings accrue from their clinical use.

ORIGIN OF LIFE FROM PROTEIN SYNTHESIS

Helpful to an appreciation of the importance of the proteins of the plasma in health and disease is the realization of the primacy of protein in the origin of life. As discussed by Oparin, biologists now generally hold that there first appeared in the water of the earth's primeval ocean various substances formed from carbon, hydrogen, oxygen and nitrogen. These were the most elementary of organic compounds.

PRECELLULAR FORMATION OF PROTEIN

During the next stage more complex substances were formed, finally resulting in the appearance of amino acids, later polypeptides and then proteins. The colloidal properties of proteins led to the subsequent formation of coacervate complexes, *i.e.*, microscopic floating droplets which have separated out of solution. Coacervates fused with one another, increased in size and complexity and ultimately developed structural organization. At this point the stage was set for the appearance of the most primordial organism. The emergence of higher and higher forms of life followed in the succeeding millennia.

The evolution of matter in this form led to proteins

becoming not only the predominant stuff of, but the precondition for, the origin of life. Proteins as protoplasm fused and became organized into biologic entities which ultimately developed cellular structure. In time their further elaboration as plasma proteins became a function of the cellular structure originally evolved from the fusion of protein.

INTERACTION OF HUMORAL AND CELLULAR FACTORS IN BLOOD

The cellular and humoral (plasma) components of the blood may also be considered from a similar point of view. Both are necessary, as platelets, fibrinogen and other plasma substances for coagulation; as leukocytes and antibodies of the globulin fraction for immunity and resistance; and as erythrocytes and albumin for circulatory homeostasis.

In general, the more highly developed the species in the evolutionary scale the greater is the total protein concentration. Such changes are also characterized by an increased ratio of albumin to globulin and the appearance of, or increase in, a globulin fraction corresponding to gamma globulin.

There is also evidence that in the development of the embryo there occur changes in the serum protein. It has been shown that in the transition from tadpole to frog there is a significant change in both the quantity and the distribution of the serum proteins. In the adult the total protein was found to be twice that of the undeveloped animal, and the albumin increased fourfold.

Most aquatic forms of animal life have a low serum protein concentration. The increase in albumin dur-