

Clinical Aspects of
THE PLASMA PROTEINS

TADASHI KAWAI, M. D.

IGAKU SHOIN LTD. TOKYO

Clinical Aspects of **THE PLASMA PROTEINS**

TADASHI KAWAI, M. D.

*Director, Central Clinical Laboratory and Research Division
Nihon University Surugadai Hospital, Tokyo*

*Professor of Clinical Pathology,
Nihon University School of Medicine, Tokyo*

*Professor of Clinical Pathology,
Jichi Medical School, Tochigi*

1973



IGAKU SHOIN LTD. TOKYO

© First Edition, 1973 by IGAKU SHOIN LTD., 5-29-11 Hongo, Bunkyo-ku, Tokyo.
All rights reserved. No part of this book may be translated or reproduced in any form by print, photoprint, microfilm, or any other means without written permission from the publisher.

Printed and bound in Japan

Foreword

It was the year of 1969 when this monograph was originally published in Japanese by Professor TADASHI KAWAI, titled as "The Plasma Proteins, Their Fundamental and Clinical Aspects." After I read through the Japanese edition, I was impressed by its rather complete coverage of the subjects and their detailed descriptions. I have felt that this excellent monograph should be distributed not only among our Japanese scientists but also among many other colleagues throughout the world. I am happy, therefore, to know that the English edition of his monograph, partly revised, is ready to be published at this time.

Professor KAWAI received his postgraduate medical training in U.S.A. for seven years, and was certified by the American Board of Pathology in both Anatomical and Clinical Pathology in Fall, 1962. Thus, I believe, he is the most suitable fellow for publishing the English edition of this kind.

The first parts of the book are concerned by the fundamental and physiological properties of the plasma proteins. The most important part of this book deals with the pathophysiology of various plasma protein abnormalities. Among innumerable clinical cases that the author has experienced for the past 15 years, more than one hundred representative cases were selected and arranged adequately in the text with most beautiful immunoelectrophoretic patterns, each being analyzed painstakingly by his own judgement. Therefore, the readers should find it valuable to understand, through various plasma protein abnormalities, the fundamentals and pathophysiology of many important disease conditions. In addition, this book makes almost encyclopedic coverage of the diseases accompanying any plasma protein abnormality. This monograph is certainly comparable to the excellent publications by WUHRMANN and WUNDERLY, RIVA, SCHULTZE and HEREMANS, and others, and further it contains many unique opinions of his own.

By writing a foreword to this remarkable book may I praise Professor KAWAI for his hard work!

July, 1973

Hidematsu Hirai

*Professor,
Department of Biochemistry,
School of Medicine,
Hokkaido University,
Sapporo, Japan*

*President,
The Society of Electrophoresis*

Preface

The plasma proteins are indispensable for maintaining many important functions of living cells, and their main functions include the maintenance of osmotic relations between the circulating blood and the tissue spaces, the buffering action of various body fluids and the transport of various important substances necessary for the living cells and of various metabolites. The abnormalities of the plasma proteins are likely to cause more or less functional disorders of the living cells, and, on the other hand, almost every pathology of the tissues may be reflected to the plasma protein changes. Therefore, detailed studies of the plasma protein changes are extremely valuable to evaluate clinically the pathophysiological background of each patient. In addition, among the body proteins, the plasma protein components are the ones most easily purified, and thus recent development in molecular biology has been mainly met with the plasma proteins.

This book is primarily concerned with the human plasma proteins for the purpose of understanding the pathophysiologic and diagnostic aspects of their abnormalities. Since cellulose acetate electrophoretic and immunoelectrophoretic techniques have been receiving a tremendously wide application in clinical medicine, attention is focused particularly upon understanding the pathophysiological backgrounds on many different serum protein electrophoretic patterns, covering as much new knowledge in protein biology as possible. The author, as a clinical pathologist, has attempted to relate various important clinical disorders not only to plasma protein changes but also to other laboratory findings at the same time.

There has been certainly not a few comprehensive literature on human plasma proteins, including "Die Bluteiweisskörper des Menschen" (F. WHURMANN and Ch. WUNDERLY), "The Plasma Proteins" (ed. by F. W. PUTNAM), "Serum Proteins and the Dysproteinemias" (ed. by F. W. SUNDERMAN, and F. W. SUNDERMAN, Jr.) "The Plasma Proteins" (ed. by H. NEURATH and K. BAILEY), "Serum Proteins in Health and Disease" (G. SANDOR), and so on. However, no such monograph had been published originally in Japanese, and the present author attempted it in as early as 1964. In 1966, however, the first volume of "Molecular Biology of Human Proteins" by H. E. SCHULTZE and J. F. HEREMANS was published. It resembled amazingly well to the image that the author had in his mind. Therefore, the author's attempt to publish the monograph was set aside at least for the following two years when the second volume of "Molecular Biology of Human Proteins" was not published as expected.

This monograph appeared originally in 1969, in Japanese, including the following major topics: the fundamental structure of proteins, the analytical methods of plasma proteins, the physico-chemical and biological properties of plasma proteins, the metabolism of plasma proteins, and the clinical abnormalities of plasma proteins. In this English edition, the whole section on the analytical methods and a portion of the other sections were removed, and the text was revised partly. However, the time lost for English translation has made the text of certain chapters less up to date than expected. For this the author asks the indulgence of the readers, but I sincerely hope that graduate students,

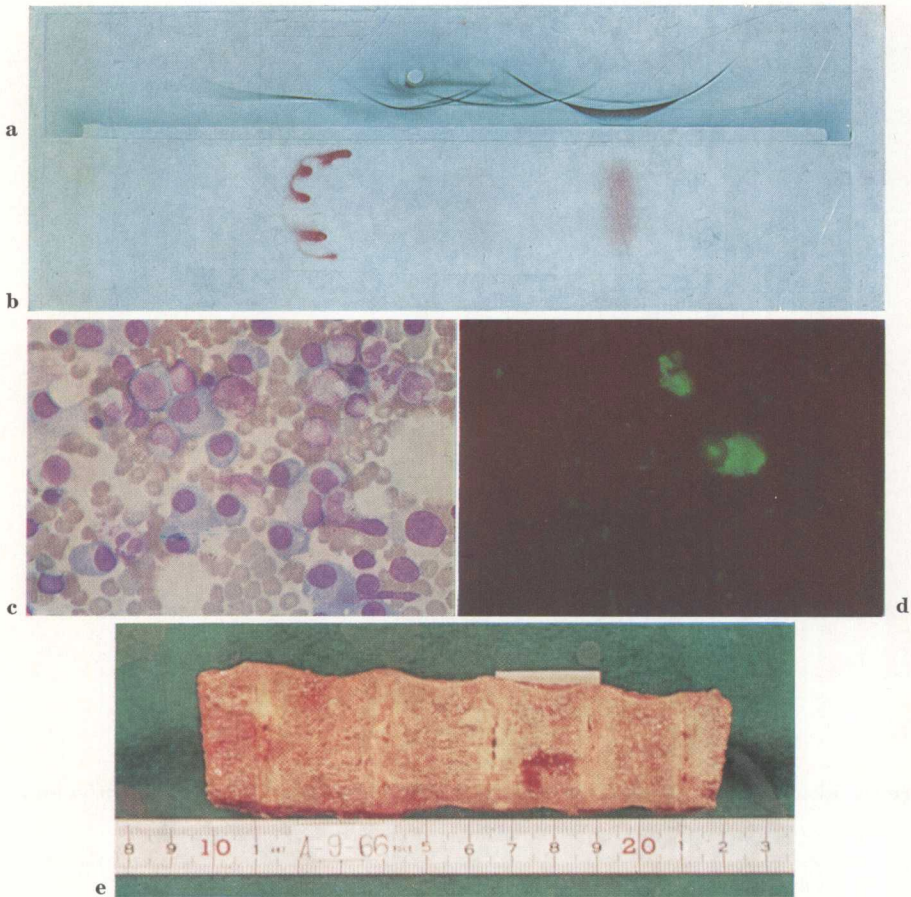
medical technologists, clinical pathologists and clinical practitioners all find this book a valuable reference for understanding the pathophysiology of plasma protein diseases and their related clinical abnormalities as well.

My greatest thanks are due to all those who have contributed in studying valuable cases cited in this book, such as many clinicians and technologists in the Central Railway Hospital of the Japanese National Railways, and the Nihon University Hospitals. I take this opportunity to express my sincere thanks also to the staff of the International Publishing Department, Igaku Shoin Ltd. for their tremendous cooperation.

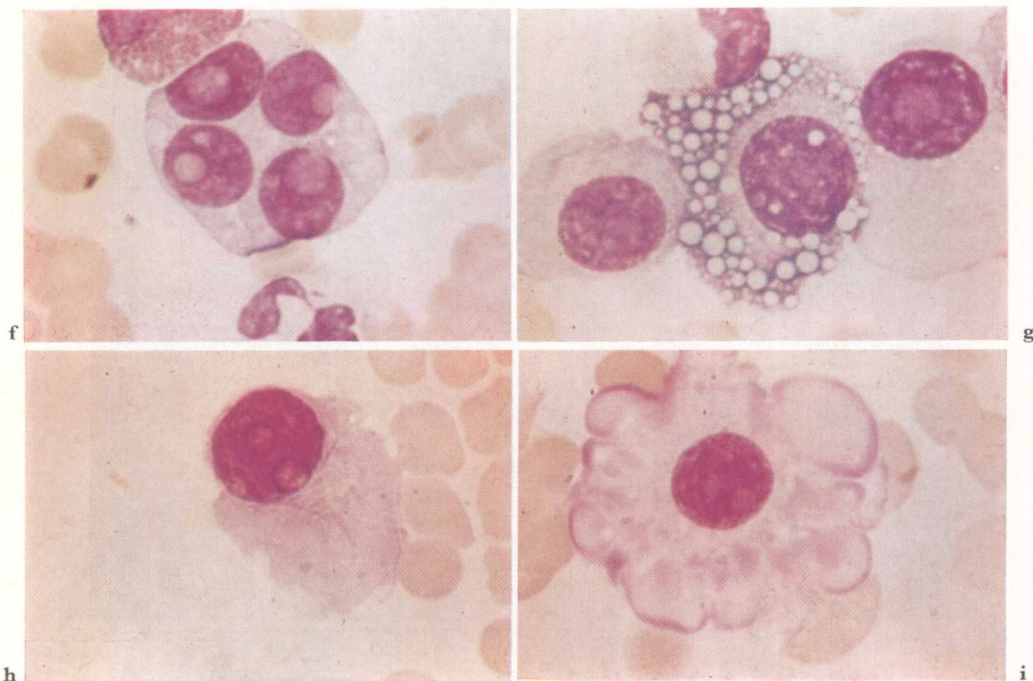
Tokyo/Japan
March, 1973

T. Kawai

Laboratory Findings in Multiple Myeloma



- a. Agar gel immunoelectrophoretic pattern of the serum taken from the patient with IgG-K type multiple myeloma. The IgG precipitin line shows a characteristic M-bow near the point of serum application. Both the IgA and IgM lines are not recognized.
- b. Cellulose acetate (Oxoid membrane) electrophoretic pattern of the same serum shows a characteristic wavy M-protein band at the cathodal end. The other protein fractions are only vaguely demonstrated because a very small quantity of the serum sample was applied.
- c. The sternal bone marrow smear obtained from the same patient shows an increased number of pleomorphic plasma cells, occupying approximately 60% of the total nucleated cells.
- d. One of the myeloma cells containing a large amount of IgG is shown through the indirect fluorescent antibody technique. Interestingly, the cell contains a positively stained inclusion body in the nucleus.
- e. The thoracic vertebrae are involved by the neoplastic change, showing an osteolytic lesion which is recognizable macroscopically.



Various kinds of the abnormal plasma cells recognized in multiple myeloma:

- f. Multi-nucleated plasma cell, containing intra-nuclear inclusion bodies.
- g. Abnormal plasma cell, containing many strongly basophilic intra-cytoplasmic inclusion bodies or Russell's bodies.
- h. Abnormal plasma cell, containing several azurophilic rods in its cytoplasm.
- i. "Flame cell" or abnormal plasma cell showing distinct peripheral eosinophilia on Giemsa staining.

Contents

Section I INTRODUCTION

Chapter 1.	THE FUNDAMENTAL STRUCTURE OF PROTEINS	3
Chapter 2.	GENERAL PRINCIPLES OF PROTEIN FRACTIONATION	6

Section II PROPERTIES OF INDIVIDUAL PLASMA PROTEIN COMPONENTS

Chapter 3.	PLASMA PROTEINS INCLUDED IN THE ALBUMIN FRACTION	11
	Albumin	11
	Prealbumin	16
Chapter 4.	PLASMA PROTEINS INCLUDED IN THE α_1 -FRACTION	18
	α_1 -Acid Glycoprotein	20
	α_1 -Antitrypsin	20
	Hormone-Binding Plasma Proteins	22
	General discussion on the hormone-binding plasma proteins	22
	Detection of the hormone-protein interaction.	22
	Physiological significance of the hormone-protein interaction	23
	Thyroxine-binding globulin (TBG)	23
	Transcortin	24
	Other α_1 -Globulins	24
	α_1 -easily-precipitable glycoprotein	24
	4.6 S-postalbumin (4.6 S PoA)	25
	Tryptophan-poor α_1 -glycoprotein (Trp α_1)	25
	α_{1X} -glycoprotein (α_{1X})	25
Chapter 5.	PLASMA PROTEINS INCLUDED IN THE α_2 -FRACTION	26
	Gc-Globulin	26
	Haptoglobin	28
	Ceruloplasmin	32
	α_2 -Macroglobulin	35
	Other α_2 -Globulins	36
	α_{2HS} -glycoprotein	37
	Zn- α_2 -glycoprotein	37

Chapter 6.	PLASMA PROTEINS INCLUDED IN THE β -FRACTION	38
	Transferrin	38
	Hemopexin	42
	$\beta_{1C/A}$ -Globulin and the Complement Components	44
	Complement system	44
	Physicochemical characteristics of the complements	44
	Biological characteristics of the complement system	47
	Clinical abnormalities	48
	Properdin	48
	Other β -Globulins	49
	β_2 -glycoprotein	49
	β_{2S} -glycoprotein	49
Chapter 7.	FIBRINOGEN AND ITS DEGRADATION PRODUCTS	50
	Fibrinogen	50
	Fibrinogen Degradation Products	53
Chapter 8.	IMMUNOGLOBULINS	56
	General Discussion on the Immunoglobulins	56
	IgG-Globulin	57
	IgM-Globulin	63
	IgA-Globulin	64
	IgD-Globulin	66
	IgE-Globulin	66
	Biological Characteristics of the Immunoglobulins	68
	Normal serum concentrations of the immunoglobulins	68
	Antibody activities of the immunoglobulins	68
	Clinical Abnormalities of the Immunoglobulins	73
Chapter 9.	GLYCOPROTEINS AND LIPOPROTEINS	74
	Glycoproteins	74
	Lipoproteins	79
	REFERENCES	90

Section III METABOLISM OF THE PLASMA PROTEINS

Chapter 10.	GENERAL SURVEY OF THE PLASMA PROTEIN METABOLISM	97
	Dynamic Equilibrium of the Plasma Protein Metabolism	97
	Principle of the Analytical Methods	100
Chapter 11.	SYNTHESIS OF THE PLASMA PROTEINS	103
	Sites of Synthesis of the Plasma Proteins	103
	Mechanisms of Synthesis of the Plasma Proteins	105
	Mechanisms of Synthetic Abnormalities of the Plasma Proteins	111
Chapter 12.	BODILY DISTRIBUTION OF THE PLASMA PROTEINS	114
	Extravascular Circulation and Distribution of the Plasma Proteins.	114

Mechanisms of Distributional Abnormalities of the Plasma Proteins.	115
Abnormalities in the tissue interstitium	115
Abnormalities due to hydrostatic changes	116
Abnormalities due to osmotic changes	116
Abnormalities due to increased capillary permeability	116
Interstitial Tissue Fluids and Edema Fluid	117
Effusions in Serous Cavities	120
Synovial Fluid	123
Cerebrospinal Fluid	125
Chapter 13. CATABOLISM OF THE PLASMA PROTEINS	131
Catabolic Rates of the Plasma Proteins	131
Sites of Plasma Protein Degradation	132
Modes of Degradation of the Plasma Proteins	132
Mechanisms of Catabolic Abnormalities of the Plasma Proteins	133
Chapter 14. EXTERNAL LOSS OF THE PLASMA PROTEINS	135
Sites of External Loss of the Plasma Proteins	135
Urinary Proteins	135
Degradation of the plasma proteins in kidneys	135
Protein pattern of normal urine	136
Protein patterns in various proteinurias	137
Plasma Proteins in Various Secretions	141
Plasma protein compositions in various types of Secretions	141
Structure and functions of the secretory IgA-globulin	143
Degradation of the plasma proteins in the gastrointestinal tract.	145
protein patterns in pathological digestive fluids	145
REFERENCES	148

Section IV DIAGNOSIS AND PATHOGENESIS OF PLASMA PROTEIN ABNORMALITIES

Chapter 15. DIAGNOSTIC APPROACHES IN PLASMA PROTEIN ABNORMALITIES	155
Clinical Symptoms in Plasma Protein Abnormalities	155
Diagnostic Application of Various Laboratory Tests	156
Chapter 16. VARIATIONS IN THE MEASUREMENT OF THE PLASMA PROTEINS	159
Artificial Variations in the Plasma Protein Measurement	159
Technical variations	159
Amount of proteins to be applied for analysis.	162
Storage or heating of serum samples	164
Increased amount of chylomicron in serum samples	165
<i>In vitro</i> hemolysis	166
Anticoagulants	171

Intravenous contrast media	172
Physiological Variations in the Plasma Protein Measurement	173
Difference between the plasma and the serum	173
Difference between the arterial and the venous bloods	173
Diurnal variation	174
Seasonal variation	175
Postural variation	177
Exertional variation	177
Variation in exhaustion	178
Nutritional variation	180
Racial variation	180
Sexual variation	181
Age variation	182
(Appendix) Plasma Proteins in the Cadavers.	184
Chapter 17. INTERPRETATION OF SERUM PROTEIN PATTERNS	186
Normal Values	186
Determination of the normal values	186
Characteristics of the normal values	187
Clinical use of the normal values	189
Representation of Serum Protein Fractional Values	189
Representation with the relative percentage (%)	189
Representation with the concentration (g/100 ml)	191
Observation of Serum Protein Electrophoretic Patterns	192
Important macroscopic observation of electrophoretic patterns	192
Informations obtained through the macroscopic observation of electrophoretic patterns	192
Differences between filter paper and cellulose acetate electrophoreses	193
Classification of the Serum Protein Electrophoretic Patterns in Diseases	193
Classifications proposed by different investigators	194
Classification of the serum protein electrophoretic patterns	196
Chapter 18. PLASMA PROTEIN CHANGES IN MALNUTRITIONAL CONDITIONS	199
Characteristics of the Malnutritional Serum Protein Electrophoretic Pattern	199
Differentiation of the Malnutritional Serum Protein Electrophoretic Pattern	200
Differentiation from the non-selective protein-losing pattern.	200
Differentiation from the acute inflammatory pattern associated with liver damage.	200
Representative Diseases Associated with the Malnutritional Serum Protein Electrophoretic Pattern	200
Poor intake of protein foods	201
Malabsorption syndrome	202
Pathophysiological Backgrounds of the Malnutritional Plasma Protein Changes.	202

Chapter 19. PLASMA PROTEIN CHANGES IN PROTEIN-LOSING CONDITIONS	204
Characteristics of the Protein-Losing Serum Protein	
Electrophoretic Patterns.	204
Serum protein electrophoretic pattern of the selective protein-losing type (the nephrotic type)	204
Serum protein electrophoretic pattern of the non-selective protein-losing type	204
Differentiation of the Protein-Losing Serum Protein	
Electrophoretic Patterns.	204
Differentiation of the non-selective protein-losing pattern.	204
Differentiation of the selective protein-losing pattern.	205
Sites and Selectivity of the Plasma Protein Loss.	206
Sites of the plasma protein loss	206
Representative diseases associated with the protein-losing patterns.	206
Selectivity of the plasma protein loss.	206
Quantitative estimation of the selectivity of the plasma protein loss	206
Nephrotic Syndrome	210
Definition and classification	210
Proteinuria in the nephrotic syndrome	211
Plasma protein changes in the nephrotic syndrome	213
Serum lipid and lipoprotein changes in the nephrotic syndrome	218
Mechanisms of the nephrotic edema	220
Plasma protein changes on treatment in the nephrotic syndrome.	221
Protein-Losing Gastroenteropathies	222
Definition and classification of the protein-losing gastroenteropathies	222
Mechanisms of the intestinal lymphangiectasia	223
Plasma protein changes in the protein-losing gastroenteropathies	223
Exudative dermatopathies	228
Serum protein patterns in burn	228
Exudative Pulmonary Diseases	231
Blood Loss and Experimental Plasmapheresis	232
Lymphorrhea and Chyluria	233
Essential Hypoproteinemia	233
Chapter 20. PLASMA PROTEIN CHANGES IN HEPATIC DISORDERS	236
Characteristics of the Hepato-Degenerative Serum Protein	
Electrophoretic Pattern.	236
Differentiation of the Hepato-Degenerative Serum Protein	
Electrophoretic Pattern.	238
Differentiation from the hyperimmunoglobulinemic pattern due to non-hepatic pathologies.	238
Differentiation of the hepato-degenerative pattern with β - γ linking	238

Representative Diseases Manifested by Serum Protein	
Patterns of Liver Injury Type	239
Hepatitis	240
Classification of hepatitis	240
Plasma protein changes in hepatitis	241
Plasma protein changes in lupoid hepatitis	246
Cirrhosis of the Liver	247
Definition and classification of the liver cirrhosis	247
Plasma protein changes in the liver cirrhosis	247
Plasma protein changes in special forms of the liver cirrhosis.	252
Obstructive Liver Diseases	252
Classification of the obstructive liver diseases	252
Plasma protein changes in the obstructive liver diseases	254
Serum lipid and lipoprotein changes in the obstructive liver diseases	254
Chapter 21. PLASMA PROTEIN CHANGES IN ACUTE PHASE RESPONSES	257
Characteristics of the Serum Protein Electrophoretic Pattern of the Acute Phase Response Type.	257
Differentiation of the Acute Phase Response Pattern.	259
Differentiation from the malnutritional pattern.	259
Differentiation from the non-selective protein-losing pattern.	259
Differentiation from the nephrotic pattern.	259
Differentiation from the pregnancy pattern.	259
Hyper- α -Glycoproteinemias and the Acute Phase Reactants	259
Pathogenesis and Classification of the hyperalpha- glycoproteinemia	259
Acute phase reactants	260
C-reactive protein	262
Hypothesis on the mechanism of increased acute phase reactants.	264
(Appendix) Effects of Hormones and Vitamins on Serum Proteins	265
Chapter 22. PLASMA PROTEIN CHANGES IN POLYCLONAL HYPERIMMOUNOGLOBULINEMIA	267
Characteristics of the Broad Hypergammaglobulinemic Serum Protein Electrophoretic Pattern.	267
Broad increase of the γ fraction	267
Changes in the modal mobility of the γ fraction	268
Changes in the serum protein fractions other than the γ fraction.	269
Representative Diseases Associated with Polyclonal Hyperimmunoglobulinemia	269
Non-Specific Protein Reactions and Serological False Positive Reactions in Polyclonal Hyperimmunoglobulinemia	273
Abnormalities in non-specific protein reactions	274
Serological false positive reactions	274

Acute and Chronic Liver Diseases	277
Chronic Infections and the Hypergammaglobulinemic State	278
Hyperimmunization, Adjuvant Disease and Sarcoidosis	279
Experimental hypersensitization	280
Adjuvant disease	280
Sarcoidosis	281
Malignancies	284
Non-reticular malignancies	284
Reticular malignancies	287
(Appendix) Non-Neoplastic Proliferation of the Reticular Tissues Associated with Hyperglobulinemia	289
Autoimmune Diseases	290
Organ-specific autoimmune diseases	293
Connective tissue diseases	296
Essential Hyperimmunoglobulinemia	301
Chapter 23. PLASMA PROTEIN CHANGES IN M-PROTEINEMIC TYPE	305
Definition and Synonyms of M-Proteinemia	305
Characteristics of the M-Proteinemic Serum Protein	
Electrophoretic Pattern.	305
Appearance of M-protein band	305
Increase of globulin fractions	307
Changes in the serum protein fractions other than the M-protein band	307
Changes in the serum immunoglobulins other than the M-protein	308
Changes of serum lipids in the M-proteinemias	309
Differentiation of the M-Proteinemic Pattern	311
Differentiation from the polyclonal hypergamma- globulinemic pattern.	311
Differentiation from artificial discrete protein peaks	311
Differentiation from sharp protein peaks of the normal globulin components.	311
Unidentified protein bands not to be neglected	311
Representative Diseases Associated with the M-Proteinemic Pattern.	312
Pathogenesis of M-Proteinemia	312
Classification and Characteristics of M-proteins	318
IgG type M-proteins	318
IgA type M-proteins	324
IgM-type M-proteins	326
IgD-type M-proteins	327
IgE-type M-proteins	332
7S IgM-type M-proteins	332
γ Type M-Proteins	332
α type M-proteins	332
μ type M-proteins	333
BENCE JONES proteins	333
Changes in the Blood and the Urine Caused by the Presence of M-Proteins	336

Changes in the blood mainly due to abnormal aggregation of the M-protein	336
Changes in the blood mainly due to abnormal solubility of the M-protein	344
Changes in the blood mainly due to abnormal interaction of the M-proteins with other plasma protein components.	351
Multiple Myeloma	352
Definition and diagnostic criteria of multiple myeloma	352
M-proteins recognized in multiple myeloma	355
IgM type myeloma	355
Primary Macroglobulinemia	355
Essential M-Proteinemias	355
Frequency of essential M-proteinemias	356
Diseases associated with the essential M-proteinemias	356
Serum protein changes in the essential M-proteinemias	357
Differentiation of the essential M-proteinemias	357
Heavy Chain Diseases	361
Mechanisms of the appearance of free heavy chain	362
γ chain disease	364
α chain disease	364
μ chain disease	364
Amyloidosis	365
Pathogenesis of amyloidosis	366
Physicochemical characteristics of amyloid	366
Serum and urinary protein changes in amyloidosis	366
Autoimmune Hemolytic Diseases	368
Idiopathic chronic cold hemagglutinin disease	369
Warm type autoimmune hemolytic anemia	373
Paroxysmal cold hemoglobinuria	373
Chapter 24. ABNORMAL PLASMA PROTEINS	374
Classification and Definition of the Abnormal Plasma Proteins	374
Abnormal Fibrinogens	374
Cryofibrinogen	375
Parafibrinogens	377
Abnormal Albumin	377
Tissue Proteins Pathologically Appearing in Plasma	378
α_2 -Globulins in renal transplantation	378
Cancer-specific proteins and α_1 -fetoprotein	379
Chapter 25. DEFECT DYSPROTEINEMIAS	380
Characteristics of the Defect-Dysproteinemic Serum Protein	
Electrophoretic Patterns	380
Analbuminemia	381
Characteristics of the analbuminemic pattern	381
Differentiation of the Analbuminemic Pattern	381
Pathophysiological background in analbuminemia	382
α_1 -Antitrypsin Deficiency	383
Characteristics of the hypo- α_1 -globulinemic pattern	383
Differentiation of the hypo- α_1 -globulinemic pattern	384

Thyroxine-Binding Globulin Deficiency	384
Anhaptoglobulinemia and Ceruloplasmin deficiency	384
Anhaptoglobulinemia	384
Ceruloplasmin deficiency	384
Atransferrinemia	386
Deficiencies of the Complement Components	388
Deficiencies of lipoproteins	388
High-density lipoprotein deficiency	388
Abetalipoproteinemia and hypobetalipoproteinemia	389
Deficiency of Fibrinogen	390
Characteristics of the plasma protein	
electrophoretic pattern of ϕ -deficient type	390
Congenital afibrinogenemia	391
Acquired afibrinogenemia	392
Immunodeficiency Syndromes	393
General survey and classification of the	
immunodeficiencies.	393
Laboratory tests necessary for diagnosis of the	
immunodeficiencies	395
Characteristics of the agammaglobulinemic serum	
protein electrophoretic pattern.	396
Primary immunodeficiencies	399
Primary immunodeficiencies without significant	
deficiency of the cell-mediated immune response	400
Primary immunodeficiencies always associated	
with significant deficiency of the cell-mediated	
immune response.	403
Secondary Immunodeficiencies	411
Chapter 26. HYPERLIPOPROTEINEMIA	415
Classification of the Hyperlipoproteinemia	415
Serum Protein Changes in the Hyperlipoproteinemia	417
Serum protein changes in the increased serum	
high-density lipoprotein.	417
Serum protein changes in the increased serum	
low-density lipoproteins.	417
Differentiation of the Hyperlipoproteinemic Serum Protein	
Electrophoretic Pattern.	420
Differentiation from the changes resulted from <i>in vitro</i>	
hemolysis.	420
Differentiation from the β type M-proteins	420
Representative Diseases Associated with Hyperlipoproteinemia	420
Primary hyperlipoproteinemia	420
Secondary hyperlipoproteinemia	421
Chapter 27. PLASMA PROTEIN CHANGES IN PREGNANT AND	
FETAL PERIODS	423
Plasma Protein Changes in Pregnancy	423
Serum protein electrophoretic pattern in normal	
pregnancy	423
Plasma protein changes in normal pregnancy and	
their pathophysiological background	423

