Plasma Proteins

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FOREWORD
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Foreword

When I started in medical school some 50 years ago, we did not learn much about serum proteins. The textbook we used in physiological chemistry devoted only a few pages to this topic. We were taught that the serum contained albumin and globulins of two kinds: euglobulin and pseudoglobulin. Fibrinogen was of course regarded as an important substance but our knowledge regarding the mechanisms involved in coagulation of the blood was minimal. It is therefore fair to state that I have myself had a chance to follow practically the whole development leading to the present state of knowledge as it is described in this book. This history has been written in a superb way by Kai Pedersen in the first chapter.

I had the good fortune to enjoy collaboration with the group that was inspired by The Svedberg and Arne Tiselius. My first study with Kai Pedersen in 1937 was connected with a problem much discussed at that time. The German clinician Bennhold was a very original investigator with great imagination. He wrote some papers on the function of the plasma proteins and especially the albumin as vehicles for smaller molecules. When these were carried on the big protein molecules, they could stay in the circulation. This idea has of course been very fruitful. Bennhold attacked the problem from many aspects and his work has remained of fundamental importance. He also studied a very interesting experiment of nature, when he found two sibs, who had genetically determined almost complete lack of serum albumin but still got along fairly well. Pedersen and I were interested in the binding of bilirubin to albumin and we studied this problem in different clinical conditions with the aid of electrophoresis and ultracentrifugation.

I also had the pleasure to follow Tiselius and Pedersen when they developed new methods and discovered new facts. At this time we thought that the new names on the different serum protein fractions alpha, beta, and gamma were very special and sophisticated. They represented facts that chiefly had a theoretical, basic interest. A few years later Tiselius came back from New York and told us, laughing, that the gamma globulins had become very popular. The women in New York were parading the streets with placards inscribed: 'We want gamma globulins'. This was during a certain phase of the polio campaign.

At first glance the reader of this book will find many things that may seem very specialized. It is evident that the presentation—attempting to be complete—has to include many seemingly trivial and unimportant facts. At the same time it is quite clear that we cannot at present imagine which facts will be discussed by everybody in a few years' time. I think that it is very important to provide the kind of presentation of the facts that Kabi has given us. Earlier this company made an excellent contribution to the postgraduate education of the doctor when it edited and distributed a monograph on blood coagulation. The new volume on plasma proteins is another work with an identical aim and I think that it should be stressed that this book is not a textbook

meant to be read from cover to cover. The reader who is more technically minded will be provided with recent and correct facts regarding methodology. It is probable that this does not interest the clinician who may enjoy reading other chapters that attempt to integrate basic chemistry with clinical application. In this way I feel that the book will be widely read because the individual will find presentations of subjects that interest him in a special way.

It may well be said that this is natural with a Swedish book on plasma proteins. Swedish investigators, from the times of Olof Hammarsten to The Svedberg and Arne Tiselius and the teams working with these men, have contributed decisive knowledge regarding these substances. The development of new methods in this field has been initiated by Swedish work on such subjects as electrophoresis, ultracentrifugation, and gel filtration. Swedish industry has been very active in the technical development and Kabi has been in the front line regarding preparation of different fractions in such a pure condition that they may be used in clinical medicine. The previous Swedish edition was very well accepted and it seems appropriate to print this English edition that has been revised and brought up to date on several points.

There has been a lively discussion regarding the most ideal form of therapy imaginable. Perhaps a chemotherapeutic preparation or an antibiotic that stops the further growth of a deadly bug? A cytostatic that slows down the growth of a malignant cell or under favourable circumstances causes 'eradication of the last cell', an expression that has recently become popular among oncologists? Personally I have always been of the opinion that we have only one really ideal form of therapy. That is substitution. When a deficiency of a certain kind is corrected, either a complicated vitamin molecule or the simple iron atom, we combine natural healing and natural sciences. Substitution is always physiological and carries no risks. All over the world it has become a fashion among the mass media to repeat endless stories about the many real or invented dangers of drugs. Under such circumstances it is easy to forget the millions of patients, whose lives have been saved, when we are talking about a few exceptions. This volume treats the possibilities of giving natural substitution. Kabi has for several decades been active in strengthening our therapeutical armament with a number of important preparations. Therefore, this presentation of the facts from many of the collaborators in the programme is of special interest. The importance of gamma globulin preparations as a prophylactic can hardly be overrated but also other plasma protein fractions have gained increasing importance. We do not need much imagination in order to expect that purified proteins of the blood will become valuable in new fields.

My guess is that some readers will find the content of the chapters somewhat unbalanced. Such things are unavoidable in a book with many authors representing completely different training and interests. Nevertheless I am sure that the book is very valuable as a source of information both for doctors practising in the field and for biochemists. Plasma proteins will be a subject with increasing importance during years to come.

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Preface

The fractionation of human blood plasma has long been one of Kabi's most important fields of interest. Today Kabi can offer a wide range of plasma protein products for therapeutic use, albumin, specific immunoglobulins, fibrinogen, specific blood coagulation factors, and several other isolated proteins for research purposes.

The development of research in clinical coagulation as a new, far-reaching and important discipline together with the ever increasing understanding of the mechanism of fibrinolysis was the background to Inga Marie Nilsson's widely used book, *Haemorrhagic and Thrombotic Diseases*, which appeared in English in 1974.

The present book, *Plasma Proteins*, is complementary to Inga Marie Nilsson's book. The scientific editors-in-chief are Birger Blombäch and Lars Å. Hanson.

We wish to express our warm thanks to the editors-in-chief and to the other contributors who through their efforts have made this book possible.

It is our hope that *Plasma Proteins* will be of use as an educational textbook and as a clinical handbook.

KABI AB
Stockholm

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History

KAI O. PEDERSEN

Proteins are essential in animal nutrition and they are therefore of fundamental importance for all living beings. This was the reason why Berzelius in 1838, in a correspondence with the Dutch chemist G. J. Mulder, proposed the introduction of the name protein. Mulder had studied a number of nitrogenous substances prepared from animal and plant material and had come to the conclusion that all these substances had one part in common. The difference in the material of different origin was explained by variation in the content of bound sulphur and phosphorus. The name protein was derived from a Greek word meaning 'of first rank' and should thus stress the primary importance of these substances.

Blood plasma is a solution consisting of a mixture of virtually hundreds of individual proteins, some of them in very small amounts. It is therefore not surprising that more than a century passed after the separation of the first proteins before enough information was obtained to allow the understanding of the finer molecular structure of this fascinating group of substances.

Now we know that proteins are macromolecules and are among the most complicated of organic molecules. They are built up from hundreds of α-amino acids linked together through so-called peptide bonds into one or several long chains (primary structure). Linus Pauling and co-workers have shown that the peptide chain is often folded in a spiral, the so-called α-helix. This spiral is stabilized by various bindings between amino acids which, due to the folding, have come relatively close together in space (secondary structure). The α-helix is folded further into a more compact tertiary structure kept together by, for instance, disulphide linkages between amino acids in different parts of the α-helix. These units may further be bound together to still larger units by interchain bridges.

The secondary and tertiary structures are of fundamental importance for the properties of the native proteins. If this delicate structure is changed, for instance by heating to 50–70°C or by adding some organic solvents to the protein solution, the properties of the protein may be profoundly changed—the protein becomes denatured.

In the middle of the nineteenth century it was found that a fraction of the plasma and serum proteins could be precipitated by dilution with slightly acidified water or by the addition of, for example, sodium chloride to saturation. This protein was given various names until finally it was called globulin. The protein remaining in solution was called albumin. At this time it was discovered by T. Graham that proteins would not pass through membranes permeable to ordinary salts. Protein solutions could therefore be freed from salts by dialysis. When dissolved, the proteins formed colloidal solutions having very large particles.

In the later half of the nineteenth century, many different separation methods were introduced into protein chemistry. It was found that a number of neutral salts would precipitate proteins reversibly without denaturation. Thus in 1879 Olof Hammarsten at