GLOMERULONEPHRITIS

Edited by
YAWARA YOSHITOSHI
YASUSHI UEDA

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Proceedings of the International Symposium on Glomerulonephritis–Progression and Regression, held December 6, 7 and 8, 1977

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Foreword

The development of modern medicine has contributed to clarifying the etiology and treatment of various diseases as well as to improving public health and welfare. However, there are many diseases of unknown etiology, for which there is no known treatment, which still leave large numbers of patients in a chronic incurable state.

Renal disease is one of these so far incurable diseases whose symptoms progress steadily and at last result in death. Its occurrence is thought to be in part genetically determined; however, new approaches to this disease are necessary. Under these circumstances, an international symposium on glomerulonephritis was held to present the results of recent research and suggestions for future work. This book is the proceedings of that symposium.

The Japan Medical Research Foundation was established to promote research on various intractable chronic diseases and to promote the development of medical science in general with aid from non-governmental financial sources.

The Foundation is very pleased to support the publication of these proceedings.

I would like to express my personal gratitude to the members of the executive committee who made the symposium possible and to the staff members who worked on these proceedings.

Masayoshi Yamamoto

President
Japan Medical Research
Foundation

Preface

Despite the development of medical science in recent years, we have no means of preventing the progression to renal failure of various renal diseases, especially glomerulonephritis. The reason for this situation is that we have not yet succeeded in clarifying the true process of progression or regression of glomerulonephritis.

The "International Symposium on Glomerulonephritis: Its Progression and Regression" was held on December 6,7 and 8, 1977, in Tokyo. The purpose was to discuss various factors related to the progression and regression of glomerulonephritis.

It was my great pleasure to hold this very exciting symposium with distinguished investigators from the U.S.A., Europe and Japan. We had ample time for very enthusiastic discussion among the participants, and it was the first chance for most Japanese nephrologists to attend such a useful international meeting in this country.

This book is the record of this International Symposium on Glomerulonephritis. I would like to express my cordial gratitude to all participants in the symposium and all members of the Executive Committee for its great success. I would also like to thank Dr. Ueda for his cooperation in editing this book.

Furthermore, I am grateful to Mr. M. Yamamoto, President of the Japan Medical Research Foundation, for his generous advice on the organization of this symposium.

I hope this book will be of use to Japanese nephrologists in coping with intractable glomerulonephritis in this country.

January 1979

Yawara Yoshitoshi, M. D.
Chairman of the Executive Committee

Opening Remarks

Ladies and Gentlemen:

As the chairman of the Executive Committee of this International Symposium on Glomerulonephritis, I would like to express our sincere gratitude to you all for your kind participation in this symposium, particularly for those who have come from abroad. I hope you will enjoy this symposium as well as your stay in Japan.

It is true that recent progress in medicine has greatly decreased the number of patients with certain diseases and has succeeded in relieving patients' suffering in many cases, but, on the other hand, in some diseases, such as chronic degenerative diseases, methods for proper management have not yet been established, and such patients are left in a miserable state for long periods without suitable treatment. Such problems have become the focus of public attention.

The Ministry of Health and Welfare of Japan has organized a research committee for each of the so-called intractable diseases and has asked specialists to investigate such diseases.

In 1972, eight new research committees were formed with the aid of research grants from the Intractable Diseases Division of the Public Health Bureau. At the same time, diseases of unknown etiology and those without specific therapies were identified as specific diseases for which intensive investigation should be begun. The number of research committees has grown to 43, including that for chronic nephritis under the chairmanship of Prof. Takeuchi and that for nephrotic syndrome under the chairmanship of Prof. Ueda.

These research activities are supported by the Japanese government. In addition, in order to support investigation and research on intractable diseases from a variety of aspects, the Japan Medical Research Foundation was founded as a civilian organization. Its activities include holding symposia on these intractable diseases. The present International Symposium on Glomerulonephritis is one of the activities of the Foundation.

Countermeasures for renal failure were initiated in Japan several years later than in the USA and Europe, but considerable progress has now been made. According to the investigations of a research committee supported by the Public Health Bureau, the most common cause of chronic renal failure in 1975 was chronic nephritis, as shown in Table 1. In addition to studying countermeasures for renal failure, many investigators are working to find a way to prevent or delay the progression from nephritis to renal failure.

When the research committee made a nationwide survey of all the hospitals

TABLE 1. Causes of chronic renal failure in Japan (1975)

Chronic nephritis	6,376
CN with nephrotic syndrome	239
Nephrosis	75
Diabetic nephropathy	354
Gout	86
SLE	75
Pyelonephritis	238
Polycystic kidney	182
Renal tuberculosis	70
Miscellaneous	447
Total	8,142

in Japan, 1,505 (28%) of the hospitals responded, among which 1,130 (21.6%) had patients with cases of chronic nephritis and 865 (16.6%) hospitals had patients with nephrotic syndromes, as shown in Table 2. Based on these figures, the total number of patients is estimated to be 160,000 for chronic nephritis and 36,000 for chronic renal failure (Table 3).

TABLE 2. Reported number of patients

		Chronic nephritis				Nephrotic syndrome			
	No. of hospital	patients (+)	patients (−)	total	recovered (%)	patients (+)	patients (−)	total	recovered (%)
1974	5,217	1,167	386	1,553	29.8	888	665	1,533	29.8
1975	5,225	1,130	375	1,505	28.8	865	640	1,505	28.8

TABLE 3. Estimated number of patients

	1974	1975
Chronic nephritis	153,000	164,000
Chronic renal failure	35,300	35,800

This particular problem is not limited only to Japanese but common to all mankind. It is hoped that this three-day discussion among participants from various countries will contribute to progress in solving this problem.

Yawara Yoshitoshi

President
Hamamatsu Medical College

Contents

I. BIOCHEMISTRY OF GLOMERULAR BASEMENT MEMBRANE AND GLOMERULONEPHRITIS

Biochemical Aspects of Basement Membrane Collagen and Procollagen

Nicholas A. KEFALIDES

SUMMARY

Basement membranes are extracellular matrices synthesized by a variety of cells which line all epithelial and endothelial surfaces. Basement membranes in the mature animal are composed of dissimilar protein subunits. One of these is a procollagen-like molecule associated with noncollagenous matrix glycoprotein(s).

An α-chain size collagenous peptide has been isolated from bovine lens capsule and glomerulus. This α-chain is released from the basement membrane by a three-step procedure: first, limited proteolysis by pepsin; second, reduction and alkylation of disulfide bonds under nondenaturing conditions of the solubilized protein; and third, a second limited proteolysis by pepsin of the reduced protein. The molecular weight of the α-chains was measured by gel filtration and gel electrophoresis to be 95,000. The α-chain forms part of a collagen triple-helix which consists of three identical chains. Newly synthesized and secreted basement membrane procollagen is not altered during or after its incorporation into the basement membrane.

Involvement of basement membranes in glomerulonephritis has raised the possibility that it may lead to functional derangement of the glomerular capillary. As yet, a correlation between capillary basement membrane changes in a variety of diseases and functional alterations in the kidney has not clearly been established nor defined.

The notion prevails that when the capillary basement membrane thickens it must necessarily be biochemically abnormal. This is an unproven hypothesis, although, as methods of analyzing the chemical structure of basement membranes become more sensitive, abnormalities in the chemical composition and structure of these substances may be demonstrated in disease.

It is obvious, therefore, that studies dealing with the chemical, metabolic and immunologic properties of normal basement membranes are necessary if we are to gain a clear insight into the pathogenesis of basement membrane alterations in disease.[1)]

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It is now well recognized that basement membranes from various tissues have several common characteristics. Although electron microscopic studies do not reveal typical collagen fibrils, chemical studies have revealed the presence of a collagenous protein rich in 3- and 4-hydroxyproline, hydroxylysine and glucosyl-galactose linked to hydroxylysine.[2] It is believed that in capillary basement membranes, as compared to lens capsule, there may be variable amounts of a noncollagen glycoprotein which interacts with the collagenous component to form a complex molecular organization.[3]

In this paper, I shall attempt to bring up to date recent developments on the structure and biosynthesis of basement membranes and particularly of basement membrane collagen and procollagen.

MATERIALS AND METHODS

The materials and methods used in the experiments cited below have appeared elsewhere.[3–10]

RESULTS

Composition of basement membranes

The chemical composition of basement membranes has been established for several tissues and species.[1,2] Tables 1 and 2 summarize the amino acid and carbohydrate composition of three representative mammalian basement membranes. Characteristic of their amino acid composition is the high content of the imino acids, proline and 3- and 4-hydroxyproline, of the nonpolar amino acid glycine, and the basic amino acid hydroxylysine. Although in most mammalian collagens the sum of proline plus hydroxyproline accounts for almost 22% of the amino acid residues, the sum of these two amino acids accounts for 14%, 17.4% and 17.7% of glomerular, lens capsule and Descemet's membranes, respectively. Similarly, whereas glycine accounts for one-third of the amino acid residues in interstitial collagens, it accounts for about one-fourth in whole basement membranes. Since hydroxyproline and hydroxylysine are found almost exclusively in interstitial collagen, one of the protein components in basement membranes must be collagenous. The lower hydroxyproline and glycine content indicates that proteins other than collagen are also present. The heterogeneity of the molecular composition of basement membranes was suggested by significant amounts of cysteine and tyrosine, by a low total amino acid content, and by the fact that in addition to glucose and galactose, hexosamine, mannose, fucose and sialic acid, sugars not present in soluble collagens, are found in basement membranes.[1,2] Solubility studies and analyses of the solubilized fractions indicate that basement membranes are composed of dissimilar protein subunits.[4] The data show that the ratio of hydroxylysine to hexosa-

TABLE 1. Amino acid composition of mammalian basement membranes[a]

	Human[3]		Canine[3]
Amino acid	Glomerulus	Lens capsule	Descemet's membrane
Hydroxylysine	24.5	34.5	20.0
Lysine	26.4	19.4	24.0
Histidine	18.7	15.2	11.6
Arginine	48.3	39.5	39.5
3-Hydroxyproline	12.0	21.3	6.8
4-Hydroxyproline	53.0	85.0	77.0
Aspartic	70.0	57.0	58.0
Threonine	40.3	31.0	36.4
Serine	54.2	43.4	42.0
Glutamic	101.3	94.4	94.0
Proline	64.1	67.3	95.0
Glycine	225.2	260.0	230.0
Alanine	58.6	40.6	53.0
Half-Cystine	22.0	21.0	11.0
Valine	36.0	33.2	45.0
Methionine	7.0	5.0	8.2
Isoleucine	28.6	32.0	28.5
Leucine	60.3	57.7	75.2
Tyrosine	20.5	13.0	21.0
Phenylalanine	28.3	29.8	25.0

[a]Residues/1,000 residues.

TABLE 2. Carbohydrate composition of mammalian basement membranes[a]

	Human[3]		Canine[3]
Carbohydrate	Glomerulus	Lens capsule	Descemet's membrane
Hexose	6.8	11.8	8.2
Glucose	2.5	5.5	3.5
Galactose	2.6	5.6	3.7
Mannose	1.7	0.7	2.0
Glucosamine	1.7	0.8	1.2
Galactosamine	0.3	0.2	0.3
Fucose	0.7	0.6	0.6
Sialic acid	1.5	0.5	0.7
Hexuronic acid	—	—	0.05

[a]Gm/100 gm

mine varies according to the conditions of solubilization. Extraction of glomerular basement membrane and Descemet's membrane with 8 M urea alone or by reduction and alkylation alone resulted in a lower hydroxylysine:hexosamine