GLOMERULONEPHRITIS
MORPHOLOGY, NATURAL HISTORY, AND TREATMENT

PART I OF TWO VOLUMES

EDITED BY PRISCILLA KINCAID-SMITH, T. H. MATHEW, AND E. LOVELL BECKER

FOREWORD BY JEAN HAMBURGER

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PART I

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Foreword

Glomerulonephritis is not only responsible for 300,000 deaths a year, but also one of the most fascinating, provocative, and informative of human diseases.

The history of our knowledge of glomerulonephritis could be taken as a model for the progress of medical understanding. Once it had been discovered that glomeruli are the prime target in many renal patients, a name was proposed for the new "disease": glomerulonephritis. Textbooks written 25 years ago describe it as a single and definite disease. "When glomerular nephritis is seen as a whole," Thomas Addis wrote in 1948, "it presents itself as a unique disease that cannot be mistaken for any other . . . [it may be followed] from a stormy beginning [acute glomerulonephritis] into what seems almost an end of trouble and from this latent stage into the degenerative terminal stage." And C. Wilson wrote a little later: "Ellis (1942) . . . followed the example of Volhard (1931) in emphasizing the distinct *courses* which glomerulonephritis may follow. *It was then possible to avoid descriptive terms based on clinical or histological features which are inconstant or non-specific.*"

This was written ten years ago, and during these ten years glomerulonephritis as a single entity has died and from its ashes have arisen a series of new distinct diseases. Because of the extensive use of renal biopsies and because of sophisticated new techniques, descriptive terms no longer must be avoided. Clinicians and pathologists have reconciled their viewpoints. They are now on the same side of the river. The natural history of a membranous nephritis or of an acute poststreptococcal nephritis now has as much individuality for the clinician as for the pathologist. Each of the new "diseases" born from the original mother-illness has received the final stamp of per-

sonality during recent years and has been assigned a place in combined clinical-pathological classifications. It has been demonstrated that serial biopsies do not show a transformation of one of these diseases into another in the same patient. When a kidney transplantation becomes necessary and when the renal allograft is affected with a recurrence of the disease, the type of the recurrent nephritis tends to be identical to that observed in the patient's own kidneys.

Everyone would have been happy with this long-expected marriage between histological and clinical classifications if a third party—immunological research—had not put a spoke in the newlyweds' wheel. Another type of classification, based on the mechanisms of the illness, was proposed: only two forms of glomerulonephritis were to be considered, one resulting from anti-GBM (glomerular basement membrane) autoimmunity and the other from antigen-antibody complex deposition. A quick diagnosis of either type was thought to be possible with immunofluorescent technique, which showed linear immunoglobulin deposits in anti-GBM nephritis and granular deposits in complex nephritis.

This attractive immunological classification was born from and perfectly expresses the main types of experimental glomerular disease. But in man it cannot be easily fitted into the clinical pathological classification born from clinical-pathological research. It clarifies neither clinical nor pathological findings. The linear anti-GBM pattern is found in a very small minority of cases only, and these cases do not represent any single definite "disease" (as defined by the lesions, symptoms, and cause), the only exception being Goodpasture's syndrome. The granular pattern is found in a variety of diseases, vastly different from one another to the clinician's eye. If the concept of "immune-complex deposition" versus "anti-GBM autoimmunity" is to be retained, the point has been reached where further elaboration is necessary to reconcile divergent clinical, pathological, and immunochemical observations.

In other words, contrary to some premature statements, glomerulonephritis today remains very much an unsolved problem.

This is why this book is so timely. Priscilla Kincaid-Smith has succeeded in gathering the various viewpoints of some of the best specialists. Their contributions and discussions clarify exactly what we know and what we still do not know about glomerulonephritis. Dr. Kincaid-Smith's book will, undoubtedly, become a reference book for all nephrologists.

Moreover, as I pointed out earlier, the study of glomerulonephritis is an informative model for many current medical problems. Between the lines of each chapter of this book the reader can find a crowd of questions that are raised not only by nephrology, but also by the whole of contemporary medicine. For example:

What should our attitude be in the face of the general tendancy to further subdivide diseases, and how should we define the limits of a "disease"?

When an immunological process is associated with a pathological lesion, are the immune phenomena always responsible for the lesion or could it be that the lesion is responsible for the immune response?

When a disease is empirically improved by a given treatment (such as immunosuppressive drugs), does this permit any pathogenic conclusion?

When one honest, serious, and careful investigator disagrees with another honest, serious, and careful investigator on the definition of a disease, the value of a classification, or the effect of a treatment, should we organize cooperative studies or should we just wait to see what time, the final judge of research, will eventually decide?

Nephrologists are fortunate people. Their field is packed with large and important problems. Their progress in action is swift. Their meetings, like the one reflected by this book, are usually productive at a time when so many meetings are not. And, last but not least, they now have a President of the International Society of Nephrology who is not only a most distinguished and charming lady, but also—as this book demonstrates—a very active contributor to the promotion of international scientific exchanges.

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Editors' Preface

This meeting was planned to bring together experts from different parts of the world to discuss the data that has accumulated over the last decade about the morphology, natural history, and treatment of glomerulonephritis.

For 10 years or more, since the Ciba Symposium on Renal Biopsy in 1961, hundreds of patients with known morphological diagnoses have been followed, and some knowledge of the natural history of various forms of glomerulonephritis is emerging.

Before different groups can compare their experience of natural history they must have a common nomenclature and classification. This was the first task tackled at this symposium. The classification of glomerulonephritis has always been a difficult area, and Dr. Renée Habib deserves great credit for the similarity between the classification she made in 1961 and the more sophisticated classification she presented at this meeting.

Perhaps the most controversial subject discussed at the meeting was the specificity and significance of focal and segmental lesions in glomeruli in association with the nephrotic syndrome. Have those eosinophilic lesions that resemble the "fibrin cap" seen in diabetics and in pyelonephritis a special significance in relation to the nephrotic syndrome, particularly in childhood? Do they always imply a poor prognosis and resistance to steroids and immunosuppressive drugs and do they represent a separate entity or may they develop in long-standing cases previously sensitive to treatment? Do these lesions, described in the nephrotic syndrome of childhood as "hyalinose segmentaire et focale," represent the same process as the sclerosis of juxta medullary glomeruli described by Rich in 1957, or should we distinguish between sclerosis and hyalinosis? If the lesions

affect the whole glomerulus as in "global" fibrosis, does this imply a better prognosis and an increased likelihood of response to treatment? All these questions are discussed in Section II, and some are answered.

Focal proliferative glomerulonephritis and its relationship to recurrent hematuria and diffuse mesangial deposits of IgA were a far less controversial subject, although there seem to be geographic differences in the frequency with which IgA deposits are detected. This is undoubtedly one form of glomerulonephritis in which fibrin and crescent formation is seen, but opinions differ on the prognostic significance of epithelial crescents in the multitude of clinical and pathological entities in which they develop. Linear deposition of IgG implying antiglomerular basement membrane antibody is a rare finding, which usually but not invariably indicates a rapidly progressive course with or without the pulmonary features of Goodpasture's syndrome.

Poststreptococcal glomerulonephritis defined on strict clinical criteria is clearly not always a benign disease. The longer the follow-up period, the more patients show apparently progressive histological lesions, in spite of clinical resolution that adds weight to older views of latent nephritis and a gradual progression to renal failure.

Although classical descriptions do not permit cellular proliferation in membranous glomerulonephritis, the diagnostic difficulties that confront the "would-be" renal pathologist are emphasized by the great similarity in cellularity and appearance between two figures in this book, one of membranous nephritis (Figure 1, Laver and Kincaid-Smith) and another of a typical example of membranoproliferative (mesangiocapillary) glomerulonephritis (MacDonald, Figure 3). Interesting differences in experience in patients with membranous glomerulonephritis emerged at this meeting. Although most authors are agreed that the five-year prognosis is good in this disease, the sharp decline in the survival curve after five years in Cameron's study of 41 patients resulted in a 10-year survival of only 20%. This series was in sharp contrast to a study of 38 adults in Melbourne, none of whom died of renal failure and in whom the 10-year survival was more than 80%. Differences of this type make the results of treatment difficult to interpret, but remission of membranous glomerulonephritis with disappearance of proteinuria and return to a normal basement membrane, even on electron microscopy in some of the Melbourne patients, could possibly be related to enthusiastic treatment. The results of treatment in mesangiocapillary glomerulonephritis obtained with indomethacin and with combined antithrombotic and anticoagulant treatment introduced the subject of coagulation in renal disease. It is clear that nephrologists, in addition to studying immune mechanisms, must devote time to learning the language of coagulation and fibrinolysis and indeed must study all the

complicated interrelations between inflammation, complement, coagulation, and immunological mechanisms.

Although the course of mesangiocapillary (membranoproliferative) glomerulonephritis is variable when only proteinuria is present, the prognosis is worse in patients with the nephrotic syndrome. Hypertension and renal failure almost invariably presage a rapid downhill course. An apparent reversal at this stage of this chronic form of glomerulonephritis, marked by prolongation of survival, improvement in function, and disappearance of proteinuria, microscopic hematuria, and the characteristic double-contour lesions, offers some hope that we may be able to alter the natural history by treatment. Unfortunately, unless we select a group of patients in this poor prognostic category, therapeutic trials in this and other progressive forms of glomerulonephritis will have to run five years or more before we can expect to see the benefit of any form of treatment in terms of improved survival. Repeat biopsies in diffuse lesions offer a more sensitive index of change in either direction.

The importance of coagulation was clearly manifest in relation to renal disease in pregnancy and in that fascinating group of thrombotic microangiopathies that may follow pregnancy but often occurs in other situations.

In dealing with the kidney in systemic diseases, the contributors who chose their own topics in this symposium selected only Henoch-Schönlein syndrome, renal arteritis, and lupus nephritis. No startling new facts emerged, but the meeting ended with a stimulating discussion about whether Melbourne or Chicago could lay claim to the most "genuine" form of lupus nephritis. The difference in the natural history and response to treatment of lupus nephritis in these two opposite corners of the globe was only one of a number of interesting facets that pointed to the possible role of geographic factors in glomerulonephritis.

PRISCILLA KINCAID-SMITH
T. H. MATHEW
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