CHAPTER I
INTRODUCTION

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Chronic renal diseases commonly resistant to the conventional treatment appear to be the major economic burden that has a significant impact upon the patient himself, the family as well as the nation as a whole. It has been substantiated that there has been a progressive increment in the number of chronic renal patients entering an end stage renal disease during the past several decades who dependently require renal replacement therapy namely hemodialysis, continuous ambulatory peritoneal dialysis and renal transplantation[1-5]. In accordance with this observation, two crucial factors are responsible for such therapeutic failure and the progressive increment in renal patients entering end stage renal disease First, the lack of an understanding in the appropriate pathogenetic mechanism of renal disease progression and Second, the inappropriate therapeutic approach that fails to prevent the renal disease progression[6].

In respect to the pathogenetic mechanism of renal disease progression, there appears to be 2 conceptual views that link to the present conventional therapy and therapeutic failure namely the role of immunologic mechanism and the non-immunologic mechanism.

The Immunologic Mechanism of Renal Disease Progression.

This conceptual view is based on the accumulative evidence which supports the immunologic mechanism inducing a variety of glomerular diseases such as the immune complex associated with postinfectious poststreptococcal glomerulonephritis, systemic lupus erythematosus, IgA nephropathy etc. In nephrosis, there is a suggestive evidence of immunocirculatory imbalance with a predominant T-helper 1 cell (proinflammatory cytokine activity) and a defective activity of T-helper 2 cell (anti-inflammatory cytokine activity) in severe form associated with focal segmental glomerulosclerosis[7-14]. Such an immunocirculatory imbalance observed in severe nephrosis associated with focal segmental glomerulosclerosis would allow a sustained release of proinflammatory cytokines inducing proteinuria which is generally resistant to the conventional therapy with prednisolone or immunosuppressive agent.

Although the pathogenetic mechanism of renal disease progression has never been established, the preceding conceptual view of immunologic mechanism inducing glomerular injury has led to the initiation of therapeutic rationale with immunosuppressive agent such as prednisolone and / or immunosuppressive drugs to treat a variety of chronic renal diseases. The result of such therapeutic approach indicated that a group of mild clinical renal

disease without nephronal damage such as focal segmental glomerulosclerosis and tubulointerstitial fibrosis such as that observed in mesangial proliferative nephrosis, or mild form of lupus nephritis, is usually responsive to prednisolone and / or immunosuppressive. However, a group of severe renal diseases associated with focal segmental glomerulosclerosis and tubulointerstitial fibrosis are usually resistant to the immunosuppression and the clinical course is usually destined for chronic renal failure and end stage renal disease. Such a therapeutic failure in this severe form of renal disease simply implies that the immunologic role is not crucial to the pathogenetic mechanism of renal disease progression.

The Non-Immunologic Mechanism of Renal Disease Progression.

Several factors of non-immunologic mechanism have been claimed to be associated with the pathogenesis of renal disease progression namely, lipids[15-17], reactive oxygen species[18,19], proteinuria[20,21], roles of mesangial cells[22,23], podocytes or glomerular epithelial cells[24,25], growth factors such as platelet derived growth factors, transforming growth factor beta, adhesion molecules[26,27]. However, non of these mentioned factors have ever been confirmed to be the causative factor by mean of specific therapeutic strategy. It is concluded that some of these factors may contribute in part a secondary role in the pathogenesis of renal disease progression.

In 1980, the role of a hemodynamically mediated renal disease progression has been proposed by Brenner and associated. In trying to mimic a condition of chronic renal failure or a stage of reduced nephron mass, Dr. Brenner developed a renal ablation model (5/6 nephrectomized rat) in which a hemodynamic study of renal perfusion was performed in a rat with 1/6 remnant nephron[28,29]. The study revealed that there was a renal hyperperfusion to the remaining nephron and the renal arteriolar resistances were decreased. Based on his observation, Dr. Brenner concluded that the state of overperfusion to the nephron mass is likely to be associated with renal disease progression. Such a conclusion is the main obstacle to the introduction of vasodilating agent (now a main therapeutic agent) into the therapeutic armamentarium of prevention of renal disease progression for over a decade. In addition, the observation of hyperperfusion does not have any suggestive impact upon the therapeutic strategy in treating chronic renal disease.

A different conceptual view has been simultaneously taken in the late 1970 by Futrakul and associates [30,31]. In his remarks, Dr. Futrakul has consistently observed a state of renal hypoperfusion and elevated renal arteriolar resistances in association with a variety of chronic renal diseases such as steroid resistant mesangial proliferative nephrosis, diffuse proliferative nephrosis, membranoproliferative glomerulonephritis, focal segmental glomerulosclerosis, severe form of lupus nephritis. Based upon a

long observation along the clinical course of these chronic renal diseases, it comes to a conclusion that there has been a progressive reduction in renal perfusion as the disease severity progresses. Such a relationship between renal hypoperfusion and the nephronal damage has led to the therapeutic intervention with vasodilator aiming to dilate or reduce the renal arteriolar resistances and simultaneously increase the renal perfusion. The preliminary benefit of such therapeutic approach renders a supportive view that the hemodynamically mediated mechanism is crucial to the pathogenesis of renal disease progression.

The difference in hemodynamic studies observed in human clinical setting by Futrakul and the hemodynamic studies performed in renal ablation model in animal by Brenner simply implies that there is an underlying microcirculatory defect associated with human renal diseases whereas there is no such defect in the renal ablation model in animal. That the reduction in renal perfusion and hemodynamic alteration observed in chronic renal disease are indicative index of glomerular endothelial cell injury and the nature of such injury to the glomerular endothelium remains to be the major issue of interest and require further exploration.