CHAPTER VI

SUMMARY

This thesis has addressed the important issue concerning the pathogenetic mechanism of renal disease progression. It is a general consensus that treatment of chronic renal patients with particularly relevant to the renal patients associated with nephronal damage and renal functional impairment such as nephrosis associated with focal segmental glomerulosclerosis is usually unsuccessful and the patients are commonly destined for end stage renal disease. It is of notion that there has been a progressive increment in number of chronic renal patients that become dependent to the renal replacement therapy such as hemodialysis, continuous ambulatory peritoneal dialysis and renal transplantation. Such a finding implies that the generally believed concept of the pathogenetic mechanism of renal disease progression, from which the conventionally therapeutic rationale derived, is incorrect. Since the conventional therapy consists mainly of steroid and immunosuppression, the unresponsiveness to such therapeutic regime indicates that the immunologic mechanism is unlikely to be the crucial pathogenesis of renal disease progression.

The preceding information concerning the failure of steroid and immunosuppression in preventing the renal disease progression has led people to look at this specific issue at a different angle. In

accordance with the Eastern Concept of Philosophy which states that a normal homeostasis of a living organism is dependent upon the natural balance between the blood supply and the living organism, the relationship between the renal perfusion and nephronal structure has become the focal issue of interest. In this regard there appears to be 2 concepts of belief in the cause and effect relationship between the renal perfusion and nephronal structure. *First, the mechanism of nephronal damage induces the renal vascular injury. Second, the renal perfusion defect induces nephronal damage or renal disease progression.*

In respect to the former, it is the most popular concept that many people believe that renal tissue injury is independent to the renal blood perfusion. The renal disease progression in particularly relevant to the tubulointerstitial fibrosis is primarily affected by the proteinuria integrating with the activation of inflammatory pathway such as depicted in Figure 13 (II). Leakage of plasma protein from the glomerular permeability into the tubular lumen allows an excessive amount of protein to freely contact with the tubular epithelium and thereby induce tubular epithelial injury and consequently an inflammatory activation with release of inflammatory cytokines, adhesion molecules and reactive oxygen species. Tubular epithelial injury allows the inflammation to spread into the tubulointerstitium. In respect to this concept, the

development of tubulointerstitial fibrosis subsequently induces damage to the neighbouring renal microvasculature and renal perfusion deficit. Such a belief therefore ignores the important role of renal perfusion as a determining factor to the nephronal structure.

The second concept (Figure 13, I) regarding the important role of renal perfusion as a determinant of the nephronal structure is supported by this research study. In accordance with the first objective, it has been clearly shown that plasma from renal patients are capable of inducing endothelial cell cytotoxicity (ECC) in vitro. The magnitude of ECC varies in accord with the clinical severity. This is a substantial evidence to indicate that glomerular endothelial cell injury is likely to occur in renal patients. Since glomerular endothelial cell injury would affect its release of vasodilator, the amount of blood supplying the nephronal structure is expected to be decreased in accordance with the magnitude of clinical severity. This view confirmed by the intrarenal hemodynamic study in these renal patients render a supportive evidence that a reduction in renal perfusion can be detected in the early course of renal disease such as that observed in mesangial proliferative nephrosis before any evidence of nephronal damage such as tubulointerstitial fibrosis. It is also demonstrated that the magnitude of renal perfusion defect is greater in the severe form of nephrosis associated with focal segmental glomerulosclerosis than the mild form or mesangial proliferative nephosis.

Furthermore, it has also been substantiated that the magnitude of renal perfusion deficit would become progressive as the disease severity progresses. Thus, the preceding information has shown a cause-and-effect relationship between the renal perfusion and renal disease progression.

In accordance with the second objective, the study has indicated that there is an increase in oxidant (MDA) as well as antioxidant defect—a state of oxidant-antioxidant imbalance in nephrotic patients. Such are oxidant-antioxidant imbalance would act as an oxidative stress inducing endothelial cell cytotoxicity and dysfunction determined by the intrarenal hemodynamic study. Experimental study in animal model inducing nephronal injury can be achieved by administering the reactive oxygen species. Furthermore, suppression of endothelial cell cytotoxicity can be achieved following the correction of antioxidant defect. The preceding information provides some guidance to the pathogenetic mechanism of nephronal damage or renal disease progression. The glomerular endothelial cell dysfunction induced by the oxidative stress has a significant impact upon the hemodynamics in the renal microcirculation. The preferential constriction at the efferent arteriole induces not only the intraglomerular hypertension but also exaggeratedly reduces the peritubular capillary flow supplying the tubulointerstitium. Such a hemodynamic maladjustment is likely to

induce chronic ischemic injury to the tubulointerstitial structure. It is demonstrated that there is a spatial relationship between the magnitude of peritubular capillary flow deficit and the development of tubulointerstitial fibrosis. *The newly proposed concept of hemodynamic maladjustment secondary to the glomerular endothelial cytotoxicity and dysfunction observed in nephrosis associated with focal segmental glomerulosclerosis provides 2 crucial factors namely the oxidative stress and the vasoconstriction overactivity at the arteriolar level (mainly efferent arteriole) which culminate in the pathogenetic mechanism of renal disease progression.*

In accordance with the third objective, the newly proposed hemodynamically mediated renal disease progression provides a new therapeutic approach which includes vasodilator to correct the hemodynamic maladjustment and enhances the renal perfusion in conjunction with the antioxidant therapy in order to minimize or neutralize the oxidative stress and eventually reduce the glomerular endothelial cell cytotoxicity or dysfunction. The result of the study indicates that such a therapeutic approach improves the renal function and prevents the renal disease progression.

In conclusion, the study renders a supportive view that there is a hemodynamically mediated renal disease progression secondary to

glomerular endothelial cell cytotoxicity and dysfunction induces by oxidative stress. The correction of such defects by administering the vasodilator and antioxidant improves renal function and prevents renal disease progression in severe nephrosis commonly refractory to the conventional therapy.