Progression of Chronic Renal Disease - An Update

Pages with reference to book, From 290 To 294

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Chronic renal disease once established usually progresses to end singe renal failure even when the primary cause of the renal insufficiency is removed. This progression occurs in various clinical settings, including chronic renal allograft injury[1], vesicoureteral reflux[2], after recovery from bilateral renal cortical necrosis[3], after drug discontinuation in some patients with analgesic nephropathy[4], after initial recovery from post streptococcal glomerulonephritis[5] or acute renal failure[6], or as a consequence of a congenital reduction in nephron number, as in the case of oligemeganephronia[7] or a congenital solitary kidney[8]. A reduction in the number of functioning nephrons (where GFR is reduced to one fifth of the normal) causes eventual failure of the remaining nephron units. Much stress has been placed on immunological factors that can lead to progressive deterioration of renal functions. There are different mechanisms that can lead to progression of the disease[9] and these have been studied by various workers to halt the in-exorable decline of renal function with time. The histological yardstick to measure progressive renal disease is glomerulosclerosis[9] and chronic tubulo-interstitial damage[10]. The interstitial damage is characterized by mononuclear inflammatory cell infiltration and intratubular cast formation that eventually results in tubule atrophy accompanied by interstitial fibrosis. Clinical studies have demonstrated that progressive glomemlar injury in humans is haemodynamically mediated. Adaptive alterations in glomerular haemodynamics include hyper filtration, hypertension, hyper perfusion and hypertrophy. Dietary protein. hyperlipidaemia or systemic hypertension play an ancillary role. The tubular factors which have a significant contributary role, are hypermetabolism in the remnant nephron, interstitial calcium deposition and increased ammonia genesis.

Glomerular Factors

Glomerular Hyperfiltration

In experimental models of renal disease, a critical reduction in renal mass has been found to cause hyper filtration and intraglomerular hypertension in the remnant nephrons. Two weeks after unin ephrectomy the GFR and kidney weight increased in proportion by average of 40%[11]. Micro puncture studies in rats show that there is an increase in glomerular capillary plasma flow rate (Qa) which results in a decrease in the vascular resistance in the afferent and efferent arterioles. The fall in resistance is greater in the afferent arteriole compared to the efferent and this gives rise to an increase in the glomemlarcapillary hydraulicpressure (Pge) [11,12]. Qa and Pge account for the increase in single nephron glomerular filtration rate (SNGFR) measured in the remaining nephrons. Unilateral nephrectomy results in 40-50% increase in SNGFR[11] while SNGFR more than double with more extensive, i.e. greaterthan7O% reduction in renal mass[12]. Even after one or two decades total GFR often averages approximately 70% of the prenephrectomy values despite the 50% reduction in renal mass. This indicates that the remaining kidney is hyper filtrating. Most studies have shown that with hyperfiltration the prevalence of hypertension and proteinuria also becomes a possibility[13,14]. On the contrary, some studies have failed to support causal relationship between intraglomerular hypertension and progression of renal disease. Rats treated with doxorubicin or pummycin amnino nucleoside have been shown to develop glomemlosclerosis despite normal or reduced GFR and pressures[15]. Fine[16] proposed a new hypothesis of "glomerular tolerance". He suggested that itis not the degree of hyper filtration but the tolerance of the glomeruli to the haemodynamic stress that causes progressive renal

injury. Quantitative differences in the threshold for injury may exist between intact and diseased nephrons of the same species and between intact nephrons of different species. If glomerular tolerance could be measured, it might prove useful in identifying patients with lowered threshold for injury who are likely to be more susceptible to the adverse effects of long term glomerular hypertension. No method for detecting or quantitating such a hypothetical threshold for injury has so far been evolved. Intra-renal renin and angiotensin II have been thought to play a key role in the progression of glomemloselerosis by causing efferent arteriolar constriction and raising the intraglomerular capillary hydraulic pressure[9]. Angiotensin II also increases the trapping of macromolecules in the mesangium[17] and stimulates proximal tubular cell proliferation[18]. The beneficial effect of angiotensin II converting enzyme inhibitors on the progression of renal disease may be related to this mechanism. Of the glomemlar haemodynamic determinants of adaptive hyperfiltration, glomerular capillary hypertension probably plays the key role in the eventual structural injury.

Systemic hypertension

It may cause, as well as be a consequence of chronic renal disease. Previously it was thought that hypotension leads to glomerular sclerosis due to ischaemia where there was decreased glomenmlar perfusion resulting from renal vascular disease. More recent data has suggested that glomerular sclerosis could occur in the absence of arteriosclerotic disease and in many cases glomerular capillary hyperper fusion and hypertension could initiate glomemlar structural injury[19]. Systemic hypertension is not required for the development of glomerular capillary hyper filtration and hypertension. In diabetic rats a pathological reduction in afferent arteriolar resistance leads to an increase inglomemlarcapillary flow and allows a greater fraction of systemic blood pressure to be transmitted into the glomerular capillary network. This raises the glomerular capillary hydraulic pressure inspite of normal renal perfusion pressure[20,21]. Systemic blood pressure tends not to decline with protein rcstriction but glomerular injury is arrested[22,16]; this emphasizes the importance of glomerular than systemic haemodynamics. Studies have also shown that it is glomerular capillary hypertension rather than hyperfiltration or hyperperfusion which is the critical detenninant of glomerular cell injury. Thus control of glomerular capillary pressure may concur renal protection even in the lace of the continued systemic hypertension. The factors that increase glomemlar capillary hydraulic pressure experimentally were: a high protein diet, dietary cholesterol supplementation[27], administration of glucocorticoids[28], minerallocorticoids[29,30] or erythropoitin[31]. There arc various studies %vhich defined the role of angiotensin converting enzymes inhibitors in not only controlling blood pressure but also limiting proteinurea and slowing development of glomerular sclerosis in experimental models. ACE inhibitors normalized both systemic and glomerular capillary pressure[32-37] and thereby they are most consistently beneficial in slowing progression of experimental renal disease. The role of calcium channel blocker[5] is still under study and various studies have shown conflicting result of this family of drugs[38-44]. Several other drugs like a diuretic, vasodilator or centrally acting agent or a combination of the three have also been used though there have been very good control of blood pressure with the above drugs. Renal protection has been quite variabic with this regimen[45]. Beta adrenergic blockers have also been studied widely but the results available are not very encouraging. The deleterious consequences of intra-glomemlar hypertension besides its direct destmctive effect, have been suspected to be due to glomerular endothelial damage. This in turn may precipitate intra-glomerular coagulation[46] and increase the mesangial "trafficking" of macromolecules which promote glomemlosclerosis[46]

Role of Dietary Proteins

Protein restriction in rats with subtotal renal ablation or streptozotocin-induced diabetes mellitus is associated with a reduction in the functional and structural changes which are known to cause progressive renal failure[47]. Dietary restriction of protein has been shown to blunt the hyperfiltration

response and to reduce glomerular hypertrophy[47] There is also a decrease in serum lipid levels[48] and a reduced immune cell activation[49], both of which are known to contribute to nephrosclerosis. Kidney size, structure and function are markedly influenced by protein intake. When animals are continuously fed on protein rich diet there is an increase in their renal blood flow and GFR which is accompanied by renal hypertrophy21,50. These haemodynamics and structural cha9es canbe reversed with dietary protein restriction. Studies[51-53] have proved that a reduction of dietary protein to 0.6g/kgm/day or even lower levels with supplementation of essential amino acids or their nitrogen free keto analogues would preserve renal function and maintain nitrogen balance. Vetter et al. [54] compared the effects of different diets on the rate of progression of CRF in 60 patients; 20 were treated by protein restriction alone, 20 by protein restriction plus a supplement of essential amino acids and 20 by the same diet plus a supplement of keto-acids. The slowest rate of disease progression was seen in the keto-acid-treated group; the rates of pmgression in the other two groups did not differ from one another. These results lead to the conclusion that protein-restricted regimens supplemented with keto-acids can in many cases retani the progression of chronic renal insufficiency toward end-stage renal disease, despite the fact that none of the studies cited included a prospectively randomized control group (with the possible exception of that by Vetteret al.). The only study reporting nepative results used a keto-acid dosage one third of the others[55]. It seems clear that better results can be achieved when treatment is begun at a relatively early stage than if it is deferred until dialysis is imminent. It also appears that keto-acid supplements are more effective in slowing the progression of renal insufficiency than essential amino acid supplements. Perhaps some metabolic effect associated with the supplement, rather than the associated protein and phosphate restriction alone, plays a role. Administration of L-arginine in diet prevents the development of hyperfiltration and ameliorates proteinuria in diabetic rats.

Hyperlipidaemia

Vascular smooth muscle cells have been considered to play a key role in the pathogenesis of atherosclerosis. Since mesangial cells bear a close resemblance to the vascular smooth muscle cells, it has been suggested that accumulation of lipids within the mesangial cells may lead to focal glomerulosclerosis[56]. Lipid trapping has been shown to stimulate mesangial cell proliferation, increase production of a basement membrane4ike material, neutralize the negative charge on the glomerular basement membrane and increase the adhesion of monocytes to the capillary endothelial cells[57]; all these are likely to enhance glomerulosclerosis. Filtered lipoprotein could precipitate in the proximal tubules with consequential tubular interstitial injury. Dietary cholesterol supplementation has been reported to induce focal and segmental glomemlar sclerosis in normal animals[27,58] and to accelerate sclerosis in rats with diversed renal disease[58,59]. Recently Rabelink et al demonstrated that Simvastatin administered to nephrotic patients for 48 weeks reduced the magnitude of proteinuria[60]. In another study, hypercholestemlemic diabetic patients with nephropathy were administered pravastatin for a period of 12 weeks. Pravastatin significantly reduced albuminuria[61]. The obvious challenge with regards to lipids and hypertension is toplan strategies (exercise[62], dietary[63,64] and pharmacologic[65,66]) for retarding the progression to chronic renal failure. In this regard the most promising strategies are vasoactive and hypolipidemic agents. Vasoactive agents currently being used are calcium antagonist, angiotensin converting enzyme inhibitor and alpha blockers and those which could have great potential are endothelial inhibitors and nitrous oxide agonists.

Glomerular Hypertrophy

Enlargement of the glomemli and proximal convulated tubules accounts for the majority of the parenchymal hypertrophy[67] resulting in disproportional enlargement of the cortex in comparison to the lesser absolute hypertrophy of the renal medullaiy structure. Experimental maneuver which induce glomemlosclerosis, like unilateral nephrectomy, glucocorticoid administration and high protein diet, have been shown to promote glomerular hypertrophy. The close association between glomerular

hypertrophy and glomemlar sclerosis under experimental conditions and the absence of any evidence of a haemodynamic factor which could have caused glomerular hypertrophy[68] as led to the suggestion that under certain conditions, some local or circulating growth factor may enhance glomerular sclerosis.

Intraglomerular Coagulation

Intraglomerular fibrinoid material has been found in many forms of glomerular injury and this prompted speculation that another mechanism may be contributing to the glomemlar injury i.e., endothelial cell dysfunction leading to intra capillary thrombosis[69,70]. The administration of heparin or warfarin has been shown to reduce glomemlosclerosis in rats subjected to sub total nephrectomy[69,70]. Heparin retards the progression not only by its anti-coagulating activity but also suppresses the proliferation of mesangial cells[72]. The numerous physiological effects of heparin, however have precluded any definite conclusion as to the mcchanism of this protective effect. There should be a measure to predict the course of renal insufficiency in most patients with CRF. Serial measurement of the plasma clearance of a radioisotope(^{99m}Tc-DTPA or ^{51}Cr-EDTA) appear to be the most simple and accuratc estimate of the GFR in patients with renal insufficiency. If as in diabetic nephropathy the changes in renal function is linear the changes in the course of renal insufficiency can be analysed easily. A more simple method is to measure the decline in serial values of the reciprocal of the serum creatinine concentration. The relationship is linear in most patients after the semm creatinine rises above 2.5 mg/dl and available data indicate that spontaneous changes in the slope of the reciprocal relationship are unusual. The linearity of this relationship is consistent with reports that GFR and creatinine clearance decline at a constant rate in CRF.

Tubular Factors

The most frequently studied experimental model of chronic renal failure is the rat remnant kidney model. Maneuvers which enhance the progression of renal failure and glomerulosclerosis have been shown to produce significant tubulo-interstitial changes characterised by interstitial infiltration, fibrosis and tubular atrophy associated with active cellular hyperplasia, cellularnecrosis and cystic changes in the tubules of the remnant nephrons[9]. Several clinical studies have clearly demonstrated a close correlation between tubulointerstitial disease and renal dysfunction in different nephropathies. Moreover, morphological evaluation of human kidneys with chronic renal disease including glomerulonephritis has shown that the severity of renal impainnent, as assessed by glomemlar filtration rate, correlates better with tubulo-interstitial changes rather than with glomerular alterations[73]. These morphological findings have focussed attention on tubulointerstitial changes in the progression of renal disease.

Interstitial Calcium Deposition

Deposition of calcium salts in the renal interstitium has been shown to cause proogressive loss of renal function in rats with remnant kidneys[74]. The degree of calcification appears to correlate best with semm phosphorus levels and the deposition is thought to be due to a secondary rise in the calcium phosphorus product[75]. Lumlertgul et al.[76] observed that restriction of dietary intake to phosphorus in experimental animals was beneficial in reducing the progression of renal failure. Ibels et al. [77]. Haut et al[78] ; D\'Angelo et al. [79] have shown that in rats with surgically-induced chronic renal failure, dietary phosphate restriction may prevent hyperphosphatemia, an increase in fractional phosphate excretion, parenchymal calcification and fibrosis, renal functional deterioration and death from uremia. The most convincing evidence for a role of dietary phosphate in the progression of chronic renal failure in humans compare progression before and after instituting a low-protein (0.6 g/kg) diet in two groups of patients, one receiving 6.5 mg/kg of phosphorus and the other 12 mg/kg. Presumably, the patients were randomized, although this is not stated. Progression nearly halted in the first group but continued in the group receiving the higherphosphorus intake. In the 54 patients as a group, highly significant

correlations were noted between the rate of progression and urinary phosphate excretion or the serum level of N-terminal parathyroid hormone. Thus there is strong evidence that dietary phosphate might play an important role inprogression of CRF. Recent experimental studies have, however, shown that the well documented protective effect of phosphate restriction may be related to a fall in the glomerular filtration rate or to suppression of immune responsiveness[46]. Renal calcification is a known complication of the secondary hyperparathymidism of chronic renal failure. While thyroparathyroidectomy and selective thyroidectomy have been found useful in slowing the progression of renal failure in rat[5] with nephrotoxic serum nephritis, isolated parathyroidectomy surprisingly has no effect[79], thus implicating thyroxine as a major factor in the progression of renal disease. In a subsequent study, Conger and Falk[80] have shown that in experimental animals thyroidectomy retards the progression of renal disease by reducing intraglo merular hypertension. Thyroid replacement in these animals completely negates the protective effect of the therapy. Long term verapamil administration has been shown to decrease renal hypertrophy[81] and retard the progression of chronic renal failure, thus suggesting a potential role for Na+ICa++ exchange in the pathogenesis of progression of renal damage.

Increased Ammoniagenesis in Remnant Nephrons

Nathet al.[82] incriminated increased ammoniagenesis in the remnant nephrons as a factor in activating the complement cascade and contributing to tubulo-interstitial damage.

Tubular hypermetabolism

Schrieret al. [10] suggested that a critical reduction in renal mass in rats with remnant kidneys results in hypermetabolism in the surviving nephron population. The hypermetabolism leads to increased intra-cellular sodium concentration which activates Na+/K++ ATP ase leading to increased ATP utilisation, mitochondrial CO2 consumption and free oxygen radicle generation. The free oxygen radicles lead to lipid peroxidation and tissue damage. The increased intracellular sodium content also activates Na+/Ca++ exchange. The rise in intracellular calcium increases phospholipase activity which causes tissue damage. Phospholipase activity is also enhanced by intracellular alkalinization due to increase in Na+/H+ anti-porter transport per nephron under the influence of increased growth factor response. Several maneuvres like phosphate restriction[4], low protein diet[47], chronic verapamil[81] administration and hypothroidism[80] have been considered to retard the progression of renal disease by decreasing oxygen consumption and generation of free oxygen radicles[10]. The role of therapeutic modalities like the administration of glutathione, an oxygen radicle scavenger; inhibitors of xanthine oxidase, which is critical to oxygen radicle generation and amiloride analogues to inhibit the Na+/H+ anti-porter system, is still under review. In conclusion, several glomerular and tubular factors may be involved in the progression of chronic renal failure. Some of the studies reviewed here have enabled us to understand the mechanism which are likely to be of crucial importance in determining the progression of renal damage in spite of no further external insult to the kidney function after the initial injury.

References

1.Brenner, B. M., Cohen, R. A. and Milford, E. L. In renal transplantation, one size may notfit all. J. Am. Soc. Nephrol., 1992;3:162-69.

2. Torres, V. B., Velosa, J. A., Holley, K. B. et al. The progression of vesicooreteral reflux, Ann. Intern. Med., 1980;92:776-784.

3. Kleinknecht, D., Grunfeld. J.P., Gomez. P. C. et al. Diagnostic procedures and long-term prognosis in bilateral renal cortical necrosis. Kidney Int., 1973;4:390-400.

4. Kinacid-Smith, P. Analgesic abuse and the kidney. Kidney Int., 1980;17:250-260.

5. Baldwin, D. S. Chronic glomerulonephritis: Non-immunologic mechanisms of progressive

glomerular damage. Kidney Tnt., 1 982;21:109-120.
6. Finn, W.F. Recovery from acute renal failure. In Brcnner BM, Lazarus J.M. (eda): Acute renal failure, 2nd ed, New York, Churchill Livingstone, 1988. pp. 875-918.
7. Royer, P., Habib, R. and Leclerc, FL. Hypoplaaic renale bilaterale avec oligomegancphronie. In Schrciner GB (ed): Proceedings of the 3rd International Congress on Nephrology, vol 2 Basel, Ksrger, 1967, pp. 25 1-275.
8. Kiprov, D. D., Colvin, RB. and McClusky, R. T. Focal and segmental glomerulosclerosis and proteinuria associated with unilateral renal agcncsis. Lab. Invest., 1982;46 :275-281.
9. Klahr, S., Schreiner, G. and lchikawa, I, The progression of renal disease. N. Engl. 3. Mcd., 1988;318:1657-66.
10. Schrier, R.W., Harris, H.C. D., Chan, L. et al. Tubular hypcrmetaboiiam as a factor in the progression of chronic renal failure. Am. 3. Kidney Dia., 1988;12:243-9.
11. Deen, W.M., Maddox, D., Roberaton, C. R. et al. Dynamics of glomerular ultrafiltration in the rat. VII. Response to reduced renal mass. Am. J. Physiol., 1974;227:556-562.
12. Hostetter, T.H., Olson, J.L., Rcnnke, H. 0. et al. Hyperfiltration in remnant nephrons: A potentially adverse response to renal ablation, Am. 3. Phyaiol..1981;241 :F85-F93.
13. Oldrizzi, L., Rugiu, C., De Biase, V. et al. The aolitary kidney: A risky situation for progressive renal damage? Am. 3. Kidney Dis., 1991;17(suppl 1):57-61.
14. Higaahihara, B., Hone, S., Takeuchi, T. et al. Long-term consequence of nephrcctomy. I. Urol., 1990; 143:239-243.
15. Fogo, A., Toshids, T., Kikuchi, T. ct al. Serial micropuncture analysis of the same nephrons in chronic renal disease (CRD): Studies in two rat models of glomerulosclerosis (GS) (Abstract). Kidney Int., 1987;31:384.
16. Fine, L. 0. Preventing the progression of human renal disease: Have rational therapeutic principles emerges? Kidney Int., 1988;33:116-28.
17. Rajj, L. and Kcsne, W.F. Glomerular messngium: Its function and relationship to angiotensin II. Am. 3. Mcd., 1985;79(Suppl 3C):24-30.
18. Norman, 3., Badie, D.B., Nord, E.P. et a!. EGF induced mitogcnesis in proximal tubular cells: Potcntiation by angiotcnsin II. Am. 3. Med., 1985;79(Suppl. 3C):24-30.
19. Anderson, S. Systemic and glomerular hypertension in progressive renal disease. Kidney lnt., 1988;34(Suppl. 25): S119-S121.
20. Hostetter, TM., Troy, J.L. and Brcnner, SM. Glomerular hemodynamica in experimental diabetes mellitus. Kidney Int., 1981;19:410-15.
21. Zatz, R., Meyer, T. W., Rannke, H. 0. ct al, Predominance of hemody namic rather than metabolic factors in the pathogenesis of diabetic glomcrulopathy. Proc. Natl. Acad. Sci. USA., 1985;83:5963-5967.
22. Hostetter, T.H., Olson, J.L., Rennke, H. G. et al. Hyperfiltration in remnant nephrons: A potentialLy adverse response to renal ablation. Am. 3. Physiol., 1981;241:F85-F93.
23. Dworkin, L.D., Hostctter, T.H., Rennkc, H.G. et al. Hemodynamic basis for glomerular injury in rats with desoxycurticosterone- salt hyperten sion. J. çlin. Invest., 1984;73:1448-1461.
24. Dworkin, L. D. and Feiner, M.D. Olomerular injury in uni- nephrectomized spontaneously hypertensive rates. A consequence of glomerular capillary hypertension. 3. Clin. Invest., 1986;77:797-809.
25. Nath, K. A., Kren, SM. and Hostetter, T.H. Dietary protein restriction in established renal injury in the rat. I. Clin. lnvest., 1986;78: 1199-1205.
26. Meyer, T. W., Anderson, S. Rennke, H. 0. et a!. Reversing glomerular hypertension stabilizes established glomerular injury. Kidney Int., 1987;31:752-759.
27. Kasiske, B.L., O'Donnell, ME, Schmitz, P. 0. et a!. Renal injury of diet-induced hypercholesterolemia in rats. Kidney Int., 1990;37:880-891.

28. Garcia, DL., Rennke, H. 0., Brcnner, 3M. et al. Chronieglucocorticoid therapy amplifies glomerular injury in rats with renal ablation. J. Clin. Invest., 1987;80:867-874.
29. Tikkanen, I., Fyhrquist, F, Miettine, A., Tomorot, T. Autologoua immune complex nephritia and DOCA- NaCl load: A new model ofhypertenaion. Acta Pathol. Microbiol. Scand., 1980;88:241-250.
30. Iversen, B.M. and Ofstad, J. Effect of hypertension on experimental glomerulonephritis in rats. Lab. Invest., 1984;50:163-73.
31. Garcia, D.L., Anderson, 5,, Rennke, Fl. 0. et Anemia leasens and its prevention with recombinant human erythropoiet.:. worsena glomerular injury and hypertenaion in rates with reduced renal masa. Proc. NatI. Acad, Sci. USA., 1988;85:6142-6146.
32. Zatz, F., Dunn, B. R., Meyer, T. W. et al. Prevention ofdiabetic glomerulopathy by pharmacological amelioration of glomerular capillary hypertension, J. Clin. Inves., 1986;77:1925-1930.
33. Anderson, S., Meyer, T. W, Rennke, H. G. Control of glomerular hypertension limits glomerular injury in rats with reduced renal mass. J. Clin. Invest., 1985;76:612-619.
34. Anderson, S., Rennke, H. 0. and Brenner, B.M. Therapeutic advantage of converting enzyme inhibitors in arresting progressive renal disease associated with systemic hypertension in the rat. 3. din. Invest., 1986;77:l993-2000.
35. Meyer, T. W, Anderson, S., Rennke, H. 0. etal. Revcrsingglomerulsrhypertcnsion stabilizes estsblishedglomerular injury. Kidney lit 1987;31:752-759.
36. Neuringer, 3. R., Anderson, S. and Brenner, 3M. The role of systemic and intraglomerular hypertension. In Mitch WE., Stein J.H (eds): The progressive nature of renal disease, 2nd ed. Contemporary issues in nephrology, New York, Churchill Livingstone, 1992; Vol. 26, pp.1-21.
37. Dworkin, L. D. Grosser, M., Feiner, H.D. et al. Renal vascular effects of antihypertensive therapy in uninephrectomized spontaneously hypertensive rates. Kidney Int., 1989;35:790-798.
38. Harris, D. C.H., Hammond, W. S., Burke, T. 3. et sl. Verapamil protects against progression ofexperimental chronic renal failure. Kidney hit., 1987;31:41-46.
39. Katsumsta, H., Suzuki, H., Ohishi, A. et at Effects of antihypertensive agents on blood pressure and progression of renal failure in partially nephrectoznized spo ntaneously hypertensive rats. Lab. Invest., 1990;62:474-481.
40. Brunner, F.P., Thiel, G., Hermie, M. eta!. Long term enalapril and verspamil in rats with reduced renal mass. Kidney Int. 1989;36:969-77.
41. Jsckson, B., Debrevi, L., Cubla, R. Preservation of renal function in the rat remnsntkidney model ofehronie renal failure by blood pressurereduetion. Clin. Exp. Phsrmacol. Physiol., 1986; 13:319-23.
42. Wenzel, U.O., Troschau, 0., Sehoeppe, W. et al. Adverse effect of the calcium channel blocker nitrendipine on nephrosclerosis in rats with rcnovascular hypertension. Hypertension, 1992;20:233-41.
43. Tolins, J.P. and Rsij, L. Comparison ofconverting enzyme inhibitor and calcium channel blocker in hypertensive glomerular injury. Hypertension, 1990;16:452-61.
44. Dworkin, L. D., Grosser, lvi, Feiner, HO. at a!. Renal vascular effects of antihypertensive therapy in uninephreetomized SIR. Kidney hit., 1989;35:798-799.
45. Raymond, C.FL, Meyer, T. W. and Brenner, EM. Nephron adaptation to renal injury: In: Brenner, B.M and Rector, F C. lids. The Kidney WEt Saunders, Philadelphia, 1986;pp. 1553-85.
46. Brenner, 3M Nephron adaptation to renal injury or ablation. Am. J. Physiol., 1985;249:F324F-337.
47. Klshr, S. and Tripathy, K. Evaluation of renal function in malnutrition. Arch. Intern. Med., 1966;118:322-5.
48. Agus, D., Mann, R., Cohn, 0. etal. Inhibitory role of dietsry protein restriction on the development and expression of immune mediated, anti-tubular basement membrane induced tubulointerstitial nephritis in rats. 3. Clin. Invest, 1985;76:930-6.
49. Hostetter, T. FL., Meyer, T. W, Rennke, H 0. et al. Chronic effects of dietsry protein on renal structure and function in the rat with intact and reduced renal mass. Kidney Int., 1986;30:509-517.
50. Mitch, W. E. The influence ofdiet on theprogression ofrenal insufficiency. Ann. Rev. Med.,

1984;35:249-264-51.
51. Mashio. 0., Oldrizzi, L. and Rugiu, C. Dietary protein manipulation. In Mitch WE, Stein ill (eds): The progressive nature of renal disease, 2nd ed. Contemporary issues in nephrology, vol 26, New York, Churchill Livingstone, 1992;pp.167-182.
52. Mitch, WE. Dietary protein restriction in chronic renal failure: Nutritional efficacy, compliance and progression of renal insufficiency. J. Am. Soc. Nephrol., 1991;2:823-831.
53. Moorehesd, J.F, Chan, M.K., El-Nshss, M. et al. Lipid nephrotoxicity in chronic progressive glomerular and tubulo- interstitial disease. Lances, 1982;11:1309-11.
54. Vetter, K., holing, PT., Kaschube I., et al. Influence of ketoacid treatment on residual function in chronic renal insufficiehcy (abstract). Kidney Int., 1983;24 (Suppl. 16)8-350.
55. Kampf D., Fischer, H.C. and Keasel, M. Efficacy of an unselected protein diet (25 0) with monor oral supply of essential amino acids and keto analogues compared with a selective protein diet (40 0) in chronic renal failure. Am. J. CIin.Nutr. 1980;33:1673- 1675.
56. Alderson, L.K., Endemann, 0., Lindsey, S. et a!. LDL enhances monoeyte adhesion to endothelial cells in vitro. Am. 3. Pathol., 1968;123:334-42.
57. Diamond, JR. and Karnovaky, Mi Exacerbation of chronic aminonucleoside nephrosisby dietary cholesterol supplementation. Kidney Int., 1987;32:671-77.
58. Diamond, JR. and Kamovsky, M.J Exacerbation of chronic aminoeleoside nephrosis by dietary cholesterol supplementation. Kidney Int., 1987,32:671-677.
59. Tolins, J.P., Stone, 3. 0. and Raij, L. Interactions of hypereholesterolemia and hypertension in initiation ofglomerular injury. Kidney Int., 1992;41:1254-61.
60. Rabelink, A. J. Hene, R. J., Erkelcns, OW. et al. Partial remission of nephrotic syndrome in patients on long-term simvastin. Lancer, 1990;335 :1045-46.
61. Harris, K.P. and Pukerson, M.L. Amelioration of proteinuria with pravastain in hypereholesterolemic patients with diabetes mellitus. Jpn. J. Med., 1990;29: 150-63.
62. Exercise and HDL. Harvard Health Letter 17, No. 10, August, 1992.
63. Kusek, 3. W, Csggiula, A. W, Williams, 0. W. et al. An overview of the modification of diet in renal disease study. Contrib. Nephrol., 1990;81:50-60.
64. Klahr, S. Low protein diets and angiotensin-converting enzyme inhibition in progressive renal failure. Am. J. Kidney Dir., 1993;21 :1521-57.
65. Bjork, S., Mulec, H., Johnsen, S. A. et al. Renal protective effect of enalspril in diabetic nephropathy. Br. Med. J., 1992;304:339-43.
66. Spitalewitz, S., Porush, J. 0., Cattran, D. et sI. Treatment of hypcrlipidemia in the nephrotic syndrome. The effects ofprsvsstsin therapy. Am. J. Kidney Dis., 1993;21:I43-50.
67. Hayslert, J.P., Kashgsrian, M. and Epstein, F. H. Functional correlates of compensatory renal hypertrophy. J. Clin. Invert., 1968;47:774-82.
68. Ichikswa, 1, Yoshida, Y. and Logo, A. Glomerularhyperfiltrstion. Hyperperfusion or hypertension does not mediate the hypertrophy of glomeruli which predisposesto sclerosis. Kidney Int., 1988;33:337-39.
69. Purkerson, M.L., Hoffsten, P.E. snd Klahr, S. Pathogenesis of the glomerulopsthy associated with renal infarction inrats. Kidney Int., 1976;9:407-17.
70. Olson, J.1., Hostetter, T.H., Remake, HF. et al. Altered glomerular pemseleetivity and progressive sclerosis following extreme ablation of renal mass. Kidney Int., 1982;22:112-26.
71. Olson, 3. L Role of heparin as a protective agent following reduction of renal mass. Kidney Int., 1984;25:376-82.
72. Castellot, 3.3., Hoover, RI., Harper, P. A. et al. Heparin andglomerular epithelial cell-secreted hepsrin4ike species inhibit mesangial cell proliferation. Am. 3. Pathol., 1985; 120:427-35.
73. Mackenscn, S., Orund, K.E., Sindjic, M. et a!. Influence of the renal cortical interstitium on the serum crestinine concentration! and erestinine clearance in different selerosing interstitial nephritides.

Nephron., 1979;24:30-4.
74. lbels,L.S., Alfrey, A.C.,Haut,L. etal. Preservation offunction in experimental renal disease by dietary restriction of phosphate. N. EngI. J. Med., 1978;298:1226-6.
75. Haut, LII. and Alfrey, S.C., Gugenheim, S. et al. Renal toxicity of phosphatasc in rats. Kidney hit., 1980; 17:722-31.
76. Lumiertgul, 0., Burke, T.J., Gillium, D.M. et a!. Phosphate depletion arrests progression of chronic renal failure independent of protein intake. Kieney Int., 1986;29:658-66.
77. Ibels, L. S., Aifrey, AC., Haur, L. et al. Preservation of function in experimental renal disease by dietary restriction of phosphate. N. Engi. J. Med., 1978;298:122-26.
78. Haur, L.L., Alfrey: A. C., Gugelnhein, S. et al. Renal toxicity of phosphate in rats. Kidney Int., 1980;17:722.
79. D\'Angello, A., Bonnucci, E., Ballanti, P., etsl. Phosphate enriched dietverrus calcitonin in the prevention of osteodystrophy in experimental renal disease. Proceedings of the 6th International Workshop on Phorphste and other minerals. (In press).
80. Conger, J.D. and Falk, S.A. The protective mechanism of thyroideetomy in chronic renal failure (Abstract). Kidney Int., 1987;31:381.
81. Harris, D.C.H., Hammond, W. S., Burke, T.J. et at. Verapamil protects against progression of chronic renal failure independent ofprotein intake. Kidney Int., 1987;31 :41-6.
82. Nsthk, K.A., Hostetser, M.K. and Hostetter, T.H. Pathophysiology of chronic tubulo interstitial disease in rats. Interactions of chronic dietary reid load, ammonia and complement component C3. J. dIm. Invest., 1985;76:667-75.