NEPHROTIC SYNDROME: PRESENT STATUS. II

The previous editorial on advances in nephrotic syndrome was published in the Journal in 1971(1). Despite intense investigative efforts over the following two decades, the etiopathogenesis of idiopathic nephrotic syndrome still remains elusive. However, a great deal of information has been obtained on the underlying renal histological abnormalities, their relationship with clinical aspects and their outcome(2,3). More importantly, an impressive amount of knowledge has accumulated concerning the basic mechanisms and their derangements that may be important in the development and the progression of glomerular damage.

Immunological abnormalities(4), and molecular defects that may lead to heavy proteinuria have been extensively examined(5,6). A wide variety of inflammatory mediators and cytokines have been identified. Other substances such as leukocyte adhesion molecule(7) and endothelins(8) may have a role in modulating glomerular injury. The morphological, molecular and the antigenic structure of the glomerular capillary filter and the mechanisms of filtration of macromolecules have been elucidated. The glomerular capillary wall has both size-selective and charge-selective properties. The fenestrated endothelium, with its negative surface charge, excludes formed elements of the blood. The glomerular basement membrane with its unique organization of the collagenous lattice is the chief determinant of the permselectivity. It is particularly rich in fixed anionic sites consisting of glycosaminoglycans chiefly heparan sulfate, which impede filtration of negatively charged circulating molecules such as albumin(9). The filtration slit diaphragms also have a role in determining the ultrafiltration properties.

During childhood most cases of nephrotic syndrome are idiopathic. Quartan malaria in central Africa and hepatitis B in some east Asian countries are important causes of secondary nephrotic syndrome. Of the idiopathic cases the minimal lesion (MCNS), corticosteroid responsive variety comprises about 90-95% and is usually characterized by a prolonged course with remissions and relapses. The non-minimal group of patients are mostly resistant to corticosteroids and have a poor outcome. The etiology of MCNS and the cause of relapses remain unknown. Additionally, whereas it is likely that immunological mechanisms are important in the pathogenesis of different forms of glomerular lesions that cause heavy proteinuria, there is no knowledge of the antigens involved in most cases. No specific mode of therapy is of established benefit in such cases.

In MCNS a loss of polyanion from the glomerular capillaries may be the most proximate cause of massive hyperfiltration of albumin(2). A natural model of MCNS does not exist in animals. However, renal injury that closely resembles human MCNS can be induced in rats by a single intra-

venous injection of puromycin aminonucleoside(10). The animals develop heavy proteinuria and the ultrastructural examination of their glomeruli shows epithelial cell abnormalities and effacement of foot processes similar to those observed in MCNS(10). A loss of heparan sulfate proteoglycan from the glomeruli has been shown in puromycin aminonucleoside induced proteinuria(11).

Several immunological abnormalities have been observed in MCNS(4). The serum IgG levels are low and the antibody titers against streptococcal antigens decreased. Investigation of humoral immunity suggests activation of immune system. Unstimulated lymphocytes from the patients secrete large amounts of IgG and show cytotoxicity against cultured renal epithelial cells. Cellular immunity in MCNS has also been extensively studied(4,12). Abnormalities in the number of lymphocyte subsets such as an increase in T-suppressor cells have been found(13). Delayed hypersensitivity reactions are decreased after challenge with a variety of antigens during relapse and return to normal following remission. A decreased blast transformation by lymphocytes from the patients after exposure to mitogens has been detected. These findings suggest an abnormal suppressor cell function(4). A lymphokine termed soluble immune response suppressor (SIRS) has been detected in patients with MCNS, which is secreted by activated, circulating suppressor T lymphocytes(14). SIRS activity inhibits *in vivo* antibody production and delayed type hypersensitivity responses in a murine model. A highly cationic protein has also been detected in the blood of children with steroid responsive nephrotic syndrome(15).

The significance of various immunological perturbations in MCNS is not clear. Some of these may be a result of the nephrotic state and hyperlipidemia. It is plausible that a cytokine may directly neutralize the glomerular anionic charge or inhibit the synthesis of glycosaminoglycans or increase its degradation. Other unidentified mechanisms may be involved in the abolition of glomerular polyanion.

Although the etiology of MCNS remains obscure, its management has become more rational. The treatment is essentially based on judicious use of prednisolone. The ideal corticosteroid regimen to treat either the initial attack or the subsequent relapses is not established. The schedule employed by the International Study Group for Kidney Disease in Children (ISKD) in 1960's and subsequently adopted by most pediatric nephrologists, was based on clinical experience of the participating investigators, since no scientific studies were available. It has been suggested that the intensity of corticosteroid therapy for the initial attack may affect the frequency of relapses, and a 12-week course of daily prednisolone might be more efficacious(16). Similarly, a slow tapering of the "alternate day therapy" over 12-18 weeks may be carried out for the initial attack as well as for the relapse. Multicenter controlled studies are being carried out to examine these issues. There are no reliable criteria to predict which patient would turn out to have frequent relapses or when the relapses would cease.

Patients who develop corticosteroid related serious side effects have been mostly treated with cyclophosphamide(17) or chlorambucil(18). Both can prolong the period of remission. However, gonadal toxicity and a carcinogenic potential preclude their prolonged or repeated use. Recently there has been a renewed interest in the

use of levamisole, which can maintain a remission or reduce the number of relapses as long as it is given but on its discontinuation relapses recur(19). A few studies including our own(20) suggest that daily administration of a small dose of prednisolone for one year or more may also be effective. In the last few years cyclosporine A has been employed successfully in patients having frequent relapses with serious steroid toxicity(21). Again, the benefit lasts while this drug is being administered, and relapses occur after its stoppage. The nephrotoxicity of cyclosporine A and the unknown hazards of long term immunosuppression call for caution in its use.

Focal segmental glomerulosclerosis (FSGS), mesangial proliferative glomerulonephritis (GN) and membranoproliferative GN (MPGN) are the common lesions found in prednisolone resistant nephrotic syndrome. A very small proportion of patients with MCNS develop a morphologic transition to FSGS and steroid resistance after variable periods of a steroid responsive course(22). It has also been suggested that patients having MCNS but with mesangial deposits of IgM may have a less favorable course(23). FSGS can be observed in a number of diverse disorders such as reflux nephropathy, substance abuse and AIDS. However, patients with nephrotic syndrome having FSGS appear to form a distinct group with a poor prognosis. Some of them respond to large doses of corticosteroids and immunosuppressive drugs(24), and to cyclosporine A(25). In MPGN, prednisolone therapy on alternate days for several years(26) or even limited steroid therapy if given early(27) is reported to offer some benefit. It is not clear if such measures influence the eventual development of end stage renal disease.

It is crucial to treat patients with nephrotic syndrome with appropriate supportive measures, especially to control hypertension and prevent anasarca. Head out water immersion is effective to treat the latter and may preclude the need for albumin infusion. This simple procedure results in expansion of intravascular volume, which in turn causes release of atrial natriuretic peptide and inhibition of sodium and water reabsorption in the collecting ducts(28). Patients with heavy proteinuria and normal renal function need a high protein diet (2-3 g/kg/day) to compensate for urinary protein losses. In those with impaired renal function, associated with "non-minimal" lesions, a low protien intake (0.75 g/kg/day) has been advocated, based on the hypothesis that such a measure may decrease glomerular hyperfiltration and retard the progression of glomerular damage(29). The severity of proteinuria in these patients can be reduced with the use of angiotensin converting enzyme inhibitors such as enalapril(30), which may lead to increase in serum albumin levels and help to control edema. Serious bacterial infections and occasionally opportunistic infections remain important causes of mortality to nephrotic syndrome(31).

Most children with MCNS eventually stop getting relapses but those with significant lesions and resistance to corticosteroids usually show progression of renal injury, at widely variable pace, and develop end stage renal disease. Their problem is particularly distressing in developing countries where renal transplantation is not the usual option in children because of socioeconomic factors.

Very little progress would seem to have been made in understanding the etiopathogenesis of glomerular disorders as compared to diseases of some other organs

(*e.g.*, viral hepatitis), parly because micro-organisms do not directly cause glomerular injury. Solutions are, however, likely to emerge from research into the more basic mechanisms at the cell and molecular level.

R.N. Srivastava,
Professor, Division of Nephrology,
Department of Pediatrics,
All India Institute of Medical Sciences,
New Delhi 110 029.

REFERENCES

1. Srivastava RN. Nephrotic syndrome: present status. Indian Pediatr 1971, 10: 669-671.
2. Melvin T, Sibley R, Michael AF. Nephrotic syndrome. *In:* Pediatric Nephrology, Vol 12, Eds BM Tune, SA Mendoza, BM Brenner, JH Stein. New York, Churchill Livingstone, 1984, pp 191-230.
3. McEnery PT, Strife CP. Chronic glomerulonephritis in children. *In:* Pediatric Nephrology, Vol 12. Eds Tune BM, Mendoza SA, Brenner BM, Stein JH. New York, Churchill Livingstone, 1984, pp 231-264.
4. Schnaper HW. The immune system in minimal change nephrotic syndrome. Pediatr Nephrol 1989, 3: 101-110.
5. Madri JA, Sterzel RB. Symposium on mesangial cells and extracellular matrix (1992). Kidney Int 1992, 41: 523-694.
6. Brezis M. Forefronts in nephrology: summary of the newer aspects of renal cell injury. Kidney Int 1992, 42: 523-539.
7. Bishop GA, Hall BM. Expression of leucocyte adhesion molecules in the human kidney. Kidney Int 1989, 36: 1078-1085.
9. Kon V, Badr KF. Biological actions and pathophysiologic significance of endothelin in the kidney. Kidney Int 1992, 40: 1-12.
9. Kanwar YS. Biophysiology of glomerular filtration and proteinuria. Lab Invest 1984, 51: 7-21.
10. Diamond JR, Bonventre JV, Karnovsky MJ. A role for oxygen free radicals in aminonucleoside nephrosis. Kidney Int 1985, 478-483.
11. Mynderse LA, Hassell JR, Kleinman HK, Martin GR, Martinez-Hernandez A. Loss of heparan sulfate prteoglycan from glomerular basement membrane of nephrotic rats. Lab Invest 1983, 48: 292-302.
12. Sasdelli M, Cagnoli L, Candi P, Mandrioli M, Beltrandi E, Zuchelli P. Cell-mediated immunity in idiopathic glomerulonephritis. Clin Exp Immunol 1981, 46: 27-32.
13. Fiser RT, Arnold WC, Charlton RK, Steele RW, Childrens SH, Shirkey B. T-lymphocyte subsets in nephrotic syndrome. Kidney Int 1991, 40: 913-916.
14. Schnaper HW. A regulatory system for soluble immune response suppressor production in steroid-responsive nephrotic syndrome. Kidney Int 1990, 38: 151-159.
15. Levin M, Gascoine P, Turner MW, Barratt TM. A highly cationic protein in plasma and urine of children with steroid responsive nephrotic syndrome. Kidney Int 1989, 36: 867.
16. Brodehl J. Conventional therapy for idiopathic nephrotic syndrome in children. Clin Nephrol 1991, 35 (Suppl 1): S8-S15.
17. Srivastava RN, Agarwal RK, Choudhry VP, Moudgil A, Bhuyan UN, Sunderam KR. Cyclophosphamide therapy in frequently relapsing nephrotic syndrome with and without steroid dependence. Int J Pediatr Nephrol 1985, 6: 245-250.
18. Grupe WE, Makker SP, Ingleflinger JR. Chlorambucil treatment of frequently relapsing nephrotic syndrome. New Engl J Med 1976, 295: 746-749.
19. British Association for Pediatric Nephrology. Levamisole for corticosteroid-

dependent nephrotic syndrome. Lancet 1991, 1: 1555-1557.

20. Srivastava RN, Vasudev A, Bagga A, Sunderam R. Long-term, low-dose prednisolone therapy in frequently relapsing nephrotic syndrome. Pediatr Nephrol 1992, 6: 247-250.
21. Niaudet P, Habib R, Tete MJ, Hinglais N, Broyer M. Cyclosporin in the treatment of idiopathic nephrotic syndrome in children. Pediatr Nephrol 1987, 1: 566-573.
22. Srivastava RN, Agarwal RK, Moudgil A, Bhuyan UN. Late resistance to corticosteroids in nephrotic syndrome. J Pediatr 1985, 107: 66-70.
23. Bhuyan UN, Srivastava RN. Incidence and significance of IgM mesangial deposits in relapsing idiopathic nephrotic syndrome of childhood. Indian J Med Res 1987, 86: 53-60.
24. Mendoza SA, Reznik VM, Griswold WR, Krensky AM, Yorgin PD, Tune BM. Treatment of steroid-resistant focal segmental glomerulosclerosis with pulse methylprednisolone and alkylating agents. Pediatr Nephrol 1990, 4: 303-307.
25. Niaudet P, Broyer M, Habib R. Treatment of idiopathic nephrotic syndrome with cyclosporin A in Children. Clin Nephrol 1991, 35 (Suppl 1): S31-S36.
26. Tarshish P, Bernstein J, Tobin JN, Edelman Jr CM. Treatment of mesangiocapillary glomerulonephritis with alternate-day prednisone–A report of the International Study of Kidney Disease in Children. Pediatr Nephrol 1992, 6: 123-130.
27. Ford DM, Briscoe DM, Shanley PF, Lum GM. Childhood membranoproliferative glomerulonephritis type I: Limited steroid therapy. Kidney Int 1992, 41: 1606-1612.
28. Epstein M, Luutzenhiser R, Friedland E, Aceto RM, Camargo MJF, Atlas SA. Relationship of increased plasma atrial natriuretic factor and renal sodium handling during immersion induced central hypervolemia in normal humans. J Clin Invest 1987, 79: 738-745.
29. Ter Wee PM, Donker AJM. Clinical strategies for arresting progression of renal disease. Kidney Int 1992, 42 (Suppl 38): S114-S120.
30. Trachtman H, Gauthier B. Effect of angiotensin-converting enzyme inhibitor therapy on proteinuria in children with renal disease. J Pediatr 1988, 112: 295-298.
31. Srivastava RN, Moudgil A, Khurana OJ. Serious infections and mortality in nephrotic syndrome. Indian Pediatr 1987, 24: 1077-1080.