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HARVEY C. GONICK

VOLUME 15

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Preface

Here again we are impressed and even daunted by the immense universe to be explored. "What we know is a point to what we do not know." Open any recent journal of science . . . and judge whether the interest of natural science is likely soon to be exhausted.

Ralph Waldo Emerson, *Nature*

Emerson was prescient in foreseeing the never-ending succession of new revelations in science. As we approach the twenty-first century, some of the new discoveries that lie ahead may be predicted from current developments; others will surprise and amaze us. Wish lists amongst nephrologists will vary, but, for the record, my own hopes for the future include the following:

1. The ability to eliminate the (nonessential) word "essential" from the phrase "essential hypertension" by delineating precisely the pathophysiology of each form of hypertension
2. The ability to induce selective immune tolerance in man to permit transplants to be performed without need for continuous immunosuppressive drug treatment and without increased risk for infections and neoplasms
3. Further progress in the ability to identify and then block those processes that lead to progressive fibrosis and sclerosis within the kidney following inflammatory, toxic, or ischemic insults
4. Further progress in identification and integration of the physical and neurohumoral components of both the afferent and efferent limbs of the body's volume control mechanism, with the goal of designing novel approaches to modifying this mechanism in volume-altering disease states.

There are hopeful indications that progress in each of these areas is underway,

as discussed in several chapters of this issue of *Current Nephrology*. In their chapter on "Natriuretic Hormones and Sodium Homeostasis," Drs. Vardaman Buckalew and Herbert Kramer present a lucid update on the roles of ouabainlike factors and of atrial natriuretic peptide in both hypertension and edema-forming states. They also discuss the multiple forms of ouabainlike factors which have been uncovered to data as well as interactions between these factors and other volume mediators such as dopamine and arachidonic acid metabolites. Drs. Philip Halloran and Bruce Hall have provided us with an excellent overview of "Progress in the Immunobiology and Clinical Practice of Renal Transplantation." Although the goal of inducing selective immune tolerance has not yet been achieved, several new immunosuppressive drugs and monoclonal antibodies have been introduced, some of which may ultimately improve the safety margin in clinical transplantation. Included for discussion are the drugs FK-506, rapamycin, and RS-61443, as well as monoclonal antibodies to CD3 and to the interleukin-2 receptor alpha chain. Drs. Paul St. John Hammond, Steven Forland, Howard Erlanger, and Ralph Cutler, in their chapter on "Drugs and the Kidney," further explore the pharmacology of FK-506 and contrast the clinical utility, as well as the adverse effects of this drug, with cyclosporine. These authors have also provided us with a review of the effectiveness of the prostaglandin E_1 analog, misoprostol, in reducing the nephrotoxic effects of cyclosporine.

As new authors for *Current Nephrology,* I am pleased to welcome Drs. Claudio Ponticelli and his colleagues from the Istituto Scientifico Ospedale Maggiore, of Milano, Italy. Dr. Ponticelli and his group, who are well-known for their contributions in the treatment of membranous nephropathy, have written this year's chapter on "Glomerulonephritis."

As always, I wish you pleasant reading.

Harvey C. Gonick, M.D.

Contents

CHAPTER 1

Glomerulonephritis

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This chapter is focused mainly on the clinical aspects of primary and secondary glomerulonephritis. Noninflammatory glomerular disease, such as thrombotic microangiopathy, renal amyloidosis, myeloma kidney, etc., are covered in other chapters of this book. Numerous excellent experimental investigations have been performed in the last year. Most of these studies will not be considered in this chapter, however, since the main emphasis of this review is on clinical and pathologic studies in humans.

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PRIMARY GLOMERULONEPHRITIS

Minimal Change Disease

Minimal change disease accounts for more than 80% of all cases of idiopathic nephrotic syndrome in children, but is less frequent in adults. The etiology of the disease is not known. There is some evidence, however, suggesting an inherited predisposition. Lagueruela et al.[1] found that HLA-DQW2 was present in 72% of 32 steroid-sensitive children, compared with 35% of the normal controls. In half of the steroid-sensitive but none of the 10 steroid-resistant patients, one or both of two specific extended haplotypes—HLA-A1, B8, DR3, DRW52, SC01 and HLA-B44, DR7, DRW53, FC31—were identified. Levin et al.[2] found a highly cationic protein in the plasma and urine of children with steroid-sensitive nephrotic syndrome. The binding of this protein to the heparan sulfate of the glomerular capillary wall would reduce the surface negative charge that limits the passage of negatively charged macromolecules. Other studies have shown that serum of nephrotic patients contains a soluble immune response suppressor lymphokine that inhibits antibody production and delayed-type hypersensitivity responses. Schnaper[3] recently demonstrated that the production of this lymphokine is mediated by a 13,000- to 18,000-dalton protein derived from a suppressor-inducer lymphocyte. In contrast to a previous report claiming that this lymphokine was specific for steroid-sensitive nephrotic syndrome, Cheng et al.[4] found it more frequently, but not exclusively, in steroid-responsive patients. The same or similar factor(s) also may be responsible for the decreases in interleukin-2 production and T cell responsiveness found in minimal change disease independent of the activity of the disease.[5] Whether these factors actually are involved in the pathogenesis of minimal change disease or merely are epiphenomena of the nephrotic state is still in question. Benigni et al.[6] found that children with frequently relapsing steroid-responsive nephrotic syndrome had higher urinary thromboxane B_2 than age- and sex-matched controls. This is in agreement with the results of animal studies and suggests that thromboxane B_2 may contribute to altering the glomerular permeability to proteins in nephrosis.

Minimal change disease usually is sensitive to steroids, but a few patients display either early or late steroid resistance. Most of these patients show a focal segmental glomerulosclerosis in repeat biopsies. Fogo et al.[7] showed by morphometric analysis that, among patients with minimal change disease, only those who subsequently progressed to focal segmental glomerulosclerosis had diffuse glomerular hypertrophy in the initial biopsy. This observation, which has an equivalent in several experimental settings of animal models, still must be confirmed in further clinical studies.

The value of steroid therapy is accepted universally, but there is still disagreement about the optimal therapeutic schedule. Wingen et al.[8] compared the effects of four different regimens of steroid therapy in steroid-dependent and frequently relapsing children. Long-term daily prednisone administration (2 mg/kg/day for 1

to 3 months, tapered over 3 to 6 months) prevented relapses better than did shorter and intermittent or alternate-day or daily therapies. Unfortunately, their study does not provide any information about the side effects of the different regimens. Growth retardation is a severe complication in children on long-term steroid therapy. Padilla and Brem[9] pointed out the possibility of preventing this complication by also giving alkylating agents. Along with a reduction in the relapse rate, there was a significant increase in growth rates in 12 children with frequently relapsing or steroid-dependent nephrotic syndrome following treatment with either cyclophosphamide (2 mg/kg/day) or chlorambucil (0.2 mg/kg/day) plus prednisone (1.5 mg/kg every other day) for 8 to 10 weeks. In deciding whether or not to administer alkylating agents to children with minimal change disease, this beneficial effect must be balanced with the potential untoward effects, especially gonadal failure. Gandhi and Thomas[10] gave intermittent cyclophosphamide pulse treatment for 9 months to 2 frequently relapsing patients. Stable remissions without side effects were observed for the following 24 months. The efficacy and long-term safety of this approach have yet to be assessed, however, by controlled studies in large series of patients.

For frequently relapsing patients, cyclosporine has been suggested as an alternative to steroids or alkylating agents. Meyrier[11] has analyzed the experience gained so far from clinical trials encompassing 184 patients with minimal change disease treated with cyclosporine. Among steroid-sensitive patients, 85% attained remission with cyclosporine at doses between 3 and 6 mg/kg/day, even after discontinuing steroids. However, there was a trend toward a better success rate when cyclosporine was combined with low-dose prednisone as compared to cyclosporine given alone. It was of interest that cyclosporine obtained remissions in about 50% of patients resistant to other immunosuppressive treatments. Unfortunately, many patients relapsed when the drug was discontinued. Miller et al.[12] reported that remission of steroid-resistant nephrotic syndrome can be obtained with cyclosporine without significant changes in renal function, provided that this was not impaired already before treatment and that doses of cyclosporine did not exceed 5 mg/kg/day. However, occasional cases with unsuspected vascular lesions and stripe interstitial fibrosis have been documented among cyclosporine-treated patients with stable serum creatinine values. Therefore, further studies are needed before recommending the protracted use of this potentially nephrotoxic drug, even in relatively low doses.

Focal Segmental Glomerulosclerosis

Focal segmental glomerulosclerosis occurs in about 10% of children and 20% of adults with idiopathic nephrotic syndrome. The pathogenesis of this disease is still unclear. It has been postulated that, as in minimal change disease, the serum of individuals with focal segmental glomerulosclerosis contains a substance, proba-

bly a lymphokine, that might alter the permeability of the glomerular capillary wall and produce proteinuria; however, nonimmunologic factors also may play pathogenetic roles. Magil and Cohen[13] reported that, in focal segmental sclerosis, glomeruli with early segmental sclerotic lesions contain a larger number of monocytes than do uninvolved glomeruli. These data indicate that these cells are involved in the production of glomerular sclerosis. Moreover, since monocytes are involved in the pathogenesis of atherosclerosis, these findings also might suggest that there are some analogies between atherosclerosis and the early lesions of focal segmental glomerulosclerosis.

Previous studies have shown that patients with sclerotic lesions close to the hilus have a worse prognosis than those with lesions located peripherally. Recently, Morita et al.[14] observed the coexistence of hilar and peripheral lesions in the majority of 44 nephrotic children with focal segmental glomerulosclerosis or transition from one type to another in repeat biopsies. After a mean follow-up of 9 years, there were no differences in outcome for patients with peripheral and those with hilar focal segmental glomerulosclerosis. This important study reappraises the prognostic significance of the site of the sclerotic lesions. The prognostic importance of tubulointerstitial lesions, already suggested in previous studies, has been confirmed recently. By a multivariate analysis of numerous clinicopathologic parameters, Wehrmann et al.[15] found that interstitial fibrosis with tubular atrophy and nephrotic syndrome at the time of biopsy were the only variables with significant independent predictive value for the outcomes of 250 patients with focal segmental glomerulosclerosis.

The treatment of this disease is deceptive. Only 10% to 20% of patients with the nephrotic syndrome attain complete remission of proteinuria after an 8-week course of prednisone. Walker and Kincaid-Smith[16] observed a significant reduction, but not complete remission of proteinuria in nine patients with steroid-resistant nephrotic syndrome treated with cyclosporine, 5 to 8 mg/kg/day, for 4 to 6 months. Meyrier[11] recently reviewed the literature concerning the use of cyclosporine for focal segmental glomerulosclerosis. About 50% of patients treated with cyclosporine at doses of 5 to 7 mg/kg/day attained either partial or complete remission of proteinuria. Most patients relapsed when the drug was stopped. In several patients with focal segmental glomerulosclerosis whose initial biopsies already had shown vascular and/or intersitial lesions and who had had abnormal creatinine values before treatment, the histologic damage had progressed and there was further deterioration of renal function at the end of the course of treatment. Meyrier concludes that cyclosporine might be considered a "reasonable tentative treatment" for focal segmental glomerulosclerosis if restricted to cases with normal blood pressure, serum creatinine less than 170 μmol/L (1.9 mg/dL) and without significant vascular and/or interstitial lesions in the initial renal biopsy. Lack of remission after 4 months of cyclosporine or a rapid decline in renal function should lead to the discontinuation of treatment. Unfortunately, the available data say little about the long-term effects of cyclosporine, even in responding patients. In particular, it is not known whether the drug may or may not protect from pro-

gressive renal failure due to nephritis or whether it may be responsible for chronic nephrotoxicity. Well-designed, randomized, prospective trials are needed to define better the usefulness of cyclosporine in this disease.

Membranous Nephropathy

Membranous nephropathy is the most common cause of the nephrotic syndrome in adults. It is well appreciated that, in almost one fourth of cases, membranous nephropathy can be associated with other diseases, such as infections, neoplasias, or autoimmune disorders. Associations recently have been reported with giant lymph node hyperplasia[17] and pulmonary tuberculosis.[18] Meroni et al.[19] described the occurrence of membranous nephropathy in two brothers with familial sensorineural deafness. This association might reflect biochemical abnormalities of the biosynthesis of basement membranes, predisposing to implanting of immune complexes or trapping of antigens within the glomeruli, with the consequent development of membranous nephropathy. However, the association of deafness and membranous nephropathy also might be coincidental. Ross and Ahmed[20] pointed out that, in the few cases of membranous nephropathy associated with bullous pemphigoid, the severity of the skin lesions paralleled that of the renal disease. These data would suggest that antibodies against the epidermal basement membrane zone might be responsible for both the skin disorder and the renal disease. However, the skin and renal lesions might be different manifestations of a generalized autoimmune disorder.

Treatment of the disease is still controversial. To assess the effectiveness of a short course of high-dose, alternate-day prednisone, a controlled, prospective trial was organized by the Medical Research Council.[21] One hundred and seven adult nephrotic patients with membranous nephropathy were randomly assigned either to 125 mg of prednisone given every other day for 8 weeks or to placebo. At 3 years, there were no significant differences between treatment and control groups in creatinine clearance or daily excretion of protein (Fig 1). Therefore, it was concluded that, at the doses and time period used, alternate-day prednisone is of no significant benefit in the medium term. The main criticism of this study concerns the short period of treatment. It is unlikely that the course of a chronic disease such as membranous nephropathy would be altered notably by 2 months of therapy with a short-acting agent.

The possibility that a longer course of prednisone might be effective has been investigated. Fuiano et al.[22] analyzed the outcomes for 25 adult patients with stage 1 or 2 membranous nephropathy who had been treated for 6 months with prednisone. In stage 1 patients, proteinuria decreased by 84%, and renal function remained normal. In contrast, in stage 2 patients, proteinuria decreased by 47% and 7 of 18 patients developed renal insufficiency. The investigators concluded that prednisone therapy is effective only in patients with early membranous changes.