CHRONIC GLOMERULONEPHRITIS AND THE NEPHROTIC SYNDROME

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Chronic glomerulonephritis and the nephrotic syndrome are significant public health problems because they are relatively common and accounted for about 57 per cent of all deaths from renal disease in the United States in 1955.[1] In a recent study of mortality in renal disease Kessner and Florey found that the recorded crude death rates for chronic glomerulonephritis declined dramatically from a level of 75.6 per 100,000 in 1940 (total 100,000 persons), to 9.6 per 100,000 (16,000 persons) in 1955.[1] However, these authors present the view that the recorded change in rate is more apparent than real and probably reflects an increased awareness of the cardiovascular complications of chronic nephritis, and the consequent designation of chronic nephritis as a secondary rather than primary cause of death. Additional factors that are reflected in the changing patterns of the recorded causes of death include an increased awareness of the renal complications of diabetes mellitus and the increased attention given to the problem of infections of the kidneys, especially in women. Chronic glomerulonephritis remains the major cause of renal failure in young persons presenting for renal transplantation.[2]

The prolonged duration of these diseases and the resulting chronic disability, extensive medical care and costs to the community exaggerate the impact of the public health problems suggested by the incidence figures alone. Although comparable data are not available for chronic glomerulonephritis, the data supplied by Schlesinger, *et al.*, with regard to the nephrotic syndrome of childhood, a relatively less severe and less lethal form of renal disease, are of interest.[3] These in-

vestigators found that this disease, with an average duration of 3.6 years, resulted in an average of three hospital admissions per child with an average duration of 27 days per admission. The impact on requirements of medical manpower and economics of chronic glomerulonephritis and the nephrotic syndrome are in all probability considerably greater because of the extended duration of these medical problems.

The incidence and prevalence of certain chronic renal diseases in children has recently been reported as the result of a careful investigation, covering a 16-year period, and a population of one million in western New York State.[4,5] These authors found that the prevalence of nephrotic syndrome of childhood (nephrosis) was 15.7 per 100,000 children under 16 years of age in 1961. The incidence of the nephrotic syndrome was two new cases per 100,000 per year and that of chronic nephritis one new case per 100,000 per year. Similar studies of prevalence and incidence in adult populations are not available.

PREVALENCE OF PROTEINURIA

Neither the patient nor the physician has difficulty recognizing the overt symptomatology and signs of chronic renal disease that presents with gross hematuria, generalized edema or severe oliguria. However, the onset of chronic renal disease is frequently insidious, and the patient may be totally asymptomatic for months or years prior to the recognition of advanced renal failure. It is thus reasonable to attempt to develop methods and techniques that will permit earlier detection of progressive and potentially lethal renal disease.

The hallmark of chronic glomerulonephritis and the nephrotic syndrome is proteinuria, in excess of the small quantities normally excreted in the urine. Numerous retrospective studies of patients with asymptomatic proteinuria are available that suggest that proteinuria is frequently associated with kidney disease and a decreased duration of survival. Earlier studies by Diehl and McKinlay reported the prevalence of proteinuria in 20,000 college men on a single test to be 5.32 per cent.[6] Restudy of subsequent specimens in this population resulted in a decrease of prevalence to 0.1 to 0.2 per cent, indicating the frequency with which proteinuria is intermittent. Subsequent studies of similar age groups have detected abnormal proteinuria on more than one occasion in about one to two per cent of the subjects.[7,8]

Recent surveys of school-age children have demonstrated a prevalence of about five per cent with 1+ (30 mg per 100 cc urine) or

greater proteinuria on single testing.[9-12] These studies emphasize the inconstancy of proteinuria in children because upon retesting the prevalence characteristically decreases. For example, in the study by Wagner, *et al.*, only one per cent of the children retested under the same conditions had proteinuria on both tests.[11] The studies by both Freedman, *et al.*, and by Wagner, *et al.*, demonstrated an increased incidence of proteinuria in teen-aged children that reached a peak of about ten per cent at age ten in girls and at age 12 in boys.[10,11] This age-related higher incidence of proteinuria at early puberty has not been explained. Proteinuria appears to be increasingly common in persons older than sixty years,[10] a finding usually ascribed to the increased incidence of renal vascular disease in older age groups.

The Significance of Proteinuria

Interpretation of the significance of proteinuria presents numerous problems. Reference has already been made to the fact that proteinuria is frequently inconstant or intermittent. It is clear that in many patients excessive protein is excreted in the upright position and normal quantities appear in the urine collected from the supine position (orthostatic proteinuria). The problem is further complicated by the fact that orthostatic proteinuria may be intermittent or persistent. In addition, patients once found to have intermittent (and/or) orthostatic proteinuria may later develop constant proteinuria. King's studies of 531 young men (average age 20) with orthostatic proteinuria demonstrated that 20 per cent developed constant proteinuria six years later, and of these 35 per cent had hypertension or other signs of kidney disease.[13] In these studies an additional 92 young men were found to have asymptomatic continuous proteinuria and of these 56 per cent were hypertensive. King's studies and those of many others support the view that constant proteinuria is often a sign of chronic and progressive renal disease.

Other investigations also indicate that intermittent proteinuria may be a significant symptom of underlying renal disease. Muth observed significant pathologic changes compatible with glomerulonephritis in renal biopsy specimens from 31 of 51 patients with intermittent and low grade proteinuria.[14] Others have not confirmed the association of intermittent or orthostatic proteinuria with significant renal disease. Robinson, *et al.*, found significant pathologic changes in kidney biopsy specimens from about one-half of 56 young men with reproducible orthostatic proteinuria, but a five-year follow-up evaluation demonstrated no mortality and no evidence of progressive kidney disease in

these subjects.[15,16] Clearly, long-term prospective studies are needed to clarify the significance of intermittent or orthostatic proteinuria.

A recent long-term (40-year follow-up) retrospective study of college students by Levitt supports the belief that constant proteinuria is associated with a significant mortality from kidney disease.[17] His studies also indicate that the quantity of protein excreted is an important prognostic factor because higher grades of proteinuria were correlated with progressive renal disease and premature death, whereas intermittent and low-grade proteinuria were not associated with an increased mortality.

ETIOLOGIC AND THERAPEUTIC CONSIDERATIONS

Earlier detection and recognition of chronic renal disease is a reasonable goal in itself and would be an enormously important public health objective if appropriate and effective preventive or remedial therapy were available. Unfortunately too little is known of the etiology and pathogenesis of glomerulonephritis and the nephrotic syndrome to achieve these goals.

Increasing evidence is available to suggest that an immunologic basis underlies many forms of glomerulonephritis and the nephrotic syndrome.[18] Although it is clear that renal injury may be induced by immune complexes composed of antibody, antigen and complement components, the nature of the antigen(s) causing human renal disease is not known. Less commonly, renal injury is induced in man by antibody directed against renal antigen (glomerular basement membrane, and possibly others), but the mechanism of this immunopathology continues to elude investigators.[19]

Current experimental treatment programs employing immunosuppressive drugs[20] and anticoagulation therapy[21] appear to offer promise, but these therapies are themselves hazardous and have been reserved for desperately ill patients with life-threatening disease. Effective preventive therapy must await improved understanding of the disease processes.

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