Kidney International, Vol. 18 (1980), pp. 395–406

NEPHROLOGY FORUM

Isolated proteinuria in asymptomatic patients

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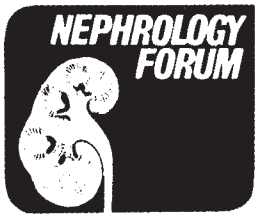
The *Nephrology Forum* is designed to relate the principles of basic science to clinical problems in nephrology.



Case presentation

A 38-year-old man was evaluated at the Duke University Medical Center for routine followup of known proteinuria for 19 years. Qualitative proteinuria was first detected during routine urinalysis when he entered military service at age 19. Repetitive examination of randomly collected urine specimens over the next several days documented the presence of proteinuria, and the patient was then admitted to Wilford Hall USAF Medical Center for further evaluation.

On admission, the patient was asymptomatic. He had no history of signs or symptoms of any form of genitourinary disease. The patient denied any prior hospitalizations or health examinations. There was no family history of kidney disease. Physical examination revealed a healthy appearing young man with a normal body build: height, 5′6″; weight, 147 lbs. Accentuated lumbar lordosis was not apparent. The supine blood pressure was 120/78 mm Hg; the remainder of the physical examination was within normal limits. Laboratory examination showed a normal hemogram including a hematocrit of 44% and an erythrocyte sedimentation rate of 9 mm/hour. Routine urinalysis was within normal limits except for 1+ proteinuria. Microscopic hematuria, pyuria, and casts were not present. Serum protein electrophoresis was normal. Blood chemistries were also normal, including a BUN of 16 mg/dl and a serum creatinine concentration of 0.9 mg/dl. Urine protein excretion was 0.64 g/day. Qualitative tests for protein on serial urine collections on 2 consecutive days revealed protein during maintenance of the quiet, upright ambulatory posture but none during recumbency. Inulin and PAH clearances in the recumbent posture were 135 and 655 ml/min/1.73 m^2 body surface area, respectively. Chest x-ray and excretory urography were normal. A percutaneous renal biopsy revealed normal renal tissue on light microscopy; electron microscopy was not performed. The patient was discharged to duty with a clinical diagnosis of "fixed and reproducible orthostatic proteinuria."

The patient remained asymptomatic without subsequent illness or hospitalization throughout the entire 19-year period. Routine followup evaluations were carried out subsequently at 4-, 9-, and 19-year intervals. At 4 years he continued to exhibit qualitative proteinuria during assumption and maintenance of a quiet upright ambulatory posture. The urine sediment was normal. The 24-hour excretion of protein was 0.42 g, and the endogenous creatinine clearance was 115 ml/min/1.73 m^2 body surface area. Maximum urine concentrating ability was normal. Physical examination at 9 years again was within normal limits. He continued to exhibit qualitative proteinuria only during the upright posture. The endogenous creatinine clearance was 98 ml/min/1.73 m^2 body surface area. At the 19-year follow-up, blood chemistries, chest x-ray, and electrocardiogram again were normal. Repeated qualitative tests of serial urine collections revealed proteinuria in the upright posture on one day, but not on another. The endogenous creatinine clearance was 145 ml/min·1.73 m_2 body surface area, and the 24-hour excretion of total protein was less than 0.08 g.

Discussion

DR. ROSCOE R. ROBINSON *(Florence McAlister Professor of Medicine, and Director, Division of Nephrology, Duke University Medical Center, Durham, North Carolina):* This man has had qualitative proteinuria for at least 19 years. Prior to his most recent examination, he always had exhibited "fixed and reproducible" orthostatic proteinuria. On his last examination in 1979, however, qualitative evidence of upright proteinuria was detected on one day, but not on another; hence, the pattern of proteinuria became "transient" or "intermittent." The sporadic presence of upright proteinuria in this patient perhaps explains why only a small amount of protein was detected on quantitative examination of a 24-hour urine sample. Qualitative proteinuria was the only clinically significant finding throughout this patient's 19-year observation period; at no time was its presence associated with urinary sediment abnormalities, evidence of a systemic disease known to affect the kidneys, or renal functional impair-

Presentation of the Forum is made possible by grants from Smith Kline & French Laboratories, Hoechst-Roussel Pharmaceuticals Inc., CIBA Pharmaceutical Company, GEIGY Pharmaceuticals, and Boehringer Ingelheim Ltd.

0085-2538/80/0018-0395 $02.40

ment. Proteinuria in this patient thus was always an "isolated" clinical phenomenon.

Diagnostic and prognostic uncertainty continue to surround the detection of qualitative proteinuria in asymptomatic individuals who seem to be in good health. The uncertainty is most pronounced when, as in this patient, the amount of proteinuria is modest, and when there is no evidence of systemic disease, impaired renal function, abnormal urine sediment, anatomic alteration as shown by excretory urography, and no history of renal or urologic disease. The unsuspected finding of qualitative proteinuria as an "isolated" event gives rise to two simple but important questions: *(1)* does proteinuria reflect the presence of underlying renal disease, and if so, *(2)* will the disease eventually cause morbidity or death? Unfortunately, neither of these questions can be answered with confidence in an individual patient because the causes and mechanisms of this type of proteinuric syndrome have not yet been clarified and are undoubtedly multiple.

Significant advances have been made in our understanding of the mechanisms of proteinuria in several experimental and clinical circumstances in the past decade. For this reason, before continuing our discussion of the clinical significance of "isolated" proteinuria, I would like to review briefly first, our present concepts regarding the manner in which a small amount of protein can enter the urine, and second, the mechanisms of pathologic proteinuria.

Excretion of protein by the healthy kidney

The daily urinary excretion of protein in apparently healthy adults is 80 ± 24 mg according to Berggard [1]. Other estimates have differed slightly, but the total daily excretion of as much as 150 mg is probably within two standard deviations of the average, and this amount therefore can be accepted as a close approximation of the upper limit of normal. Nevertheless, the relatively inexact definition of the "normal" range of total protein excreted by the healthy kidney poses a practical problem as one attempts to distinguish between normal and abnormal excretion of protein, particularly in patients with only slight proteinuria. This definition is obscured further when complicating factors such as exercise and increased catecholamine activity are present. In a healthy individual, the small amount of protein in the urine is sufficient to permit detection with the usual qualitative tests if the urine is a concentrated specimen [2, 3]. It is useful, therefore, if we have some estimate of urine concentration when considering the significance of a qualitative reaction for protein, because a concentrated urine can permit the detection of a normal amount of protein; conversely, a dilute urine can hinder the detection of an abnormal amount of protein.

Composition. Detailed analysis of the composition of normal urinary proteins requires physico- and immunochemical or radiosotopic techniques. Using these techniques, Poortman and Jeanloz have estimated that approximately 60% by weight of the total urine protein consists of normal plasma proteins in the healthy adult, whereas the remaining fraction derives directly from renal and other urogenital tissues [4]. The plasma proteins in healthy urine include albumin (about 40% of the total protein excretion), a large and heterogeneous array of small-sized immunoglobulins and their fragments, enzymes, peptide hormones, and other proteins. Normally, IgG or its fragments represents about 5% to 10% of the total urine protein, light chains comprise approximately 5%, and IgA accounts for approximately 3% (of which 90% is secretory IgA) [1, 5]; IgM and IgD are not usually detectable [1]. Thus, the proteins in healthy urine include albumin (40%), tissue proteins and antigens or glycoproteins of uroepithelial origin, for example, Tamm-Horsfall mucoproteins (40%), and immunoproteins and other plasma proteins (20%). This composition can be altered by both normal and abnormal events. For example, the increase in protein excretion after exercise is accounted for primarily by an increase in the excretion of proteins that are identical to those in plasma [4].

Anatomy of ultrafiltration. The exact anatomic location of the glomerular ultrafiltration barrier for macromolecules is uncertain. On the one hand, histochemical localization of macromolecular enzymes suggests that the filtration slit membrane between the epithelial foot processes might be the primary filtration barrier [6]; electron microscopic localization of graded dextran particles suggests, on the other hand, that the subendothelial portion of the basement membrane might be the limiting barrier [7, 8]. It seems most likely that all of the anatomic components of the capillary wall contribute to the limitation of transglomerular protein passage but that in a given experimental or clinical circumstance, molecular size, shape, or charge might be the determining factor [9]. For example, the presence of fixed glomerular anions within the endothelium and lamina rara interna might provide a major barrier to the filtration of larger circulating polyanions such as albumin, the substance of the basement membrane might restrict by size the passage of neutral macromolecules, and the slit diaphragm and lamina rara externa might prevent the passage of cationic macromolecules.

Filtration and resorption. The amount and composition of normal urine protein are primarily the net consequence of filtration by the glomeruli and subsequent tubular reabsorption of proteins. Intraepithelial production and direct addition to tubule fluid account for some of the protein in healthy urine (for example, Tamm-Horsfall protein and secretory IgA). Renal tubular secretion is another possible mechanism of proteinuria, but proof of its existence has not been established.

There is little question that most of the albumin and other plasma proteins in normal glomerular filtrate undergo subsequent renal tubular reabsorption along the nephron. Albumin concentrations of 0.1 to 3.0 mg/dl have been reported in fluid samples obtained by micropuncture from the proximal convoluted tubule and Bowman's space [10–13]. These concentrations indicate that the usual filtered load of protein far exceeds the amount in the urine; thus renal tubular reabsorption must take place along the nephron. Studies using micropuncture [11] and perfusion of isolated renal tubules [14] indicate that much of this protein is reabsorbed in the proximal tubule, although a small fraction might be reabsorbed in later nephron segments [11]. The mechanism of protein absorption, although unclear, probably involves selective endocytosis. Transport kinetics of the absorptive process are even less well understood, but some investigators have suggested that the absorptive maximum for albumin resides close to the plasma threshold, whereas the absorptive process for low-molecular-weight proteins exhibits considerable "splay" and its maximum might exceed the plasma threshold considerably [15]. In any case, when the proteins are absorbed, lysosomal combination and intracellular digestion occur and the resultant peptides or amino acids either disappear into the metabolic machinery of the cell or are returned to the contralumenal circulation. The number and nature of individual proteins that might be absorbed and returned intact to the peritubular circulation is in dispute. Similarly, controversy surrounds the magnitude of cellular uptake of protein from the peritubular circulation, although the existence of such a process seems well established, at least for certain protein hormones such as insulin [15].

Physicochemical factors. The transglomerular passage of plasma proteins has been examined in humans and experimental animals during the administration of several types of macromolecules. Dextran, a polymer of glucose with minimal tubular reabsorption, has been used most commonly. The use of dextrans of known molecular size to study the renal handling of macromolecules was pioneered by Wallenius [16] and recently was amplified by Chang et al [17–19]. Wallenius demonstrated that the glomerular filtration of dextrans decreased sharply as their effective molecular radius increased above 20 Å and that transglomerular passage was minimal at molecular sizes greater than 34 Å. Small-sized plasma proteins such as ribonuclease and lysozyme also are known to traverse the glomerular capillary walls readily. In fact, some proteins have glomerular sieving coefficients as high as 0.9 [15]. Observations such as these have suggested that glomerular filtration involves molecular sieving through the functional equivalent of aqueous pores [20]. That is, molecular size and shape are the major determinants of the transglomerular passage of macromolecules. This physical phenomenon is summarized by the term *steric hindrance,* the value of which primarily depends on the ratio of the effective radius of the solute molecule to the radius of the pore. In addition to size and shape, however, electrical forces also are involved in macromolecular passage through the glomerular capillary wall. The electrical forces are summarized by the term *electrostatic hindrance,* the phenomenon whereby the mobility of macromolecules through the glomerular wall is hindered or facilitated by electrical interactions between cationic or anionic groups on the solute and areas of charge density on the channel wall. Chang et al have demonstrated that the permeability of the normal rat glomerulus to polyanionic dextran sulfate is considerably lower than is the permeability to similarly sized molecules of neutral dextran [18]. Moreover, neutral dextrans having effective radii of 36 Å pass through the glomerular capillary wall more easily than does albumin, which has the same effective radius (36 Å), but which exists in plasma as a polyanion at physiologic pH. The addition of negatively charged sulfate radicals to the dextran molecule results in its passage across the glomerular barrier being impaired to the same degree as albumin. Conversely, the transglomerular passage of positively charged dextran molecules of the same size was facilitated [9, 21–24]. Thus, among the physicochemical factors that influence the ability of a macromolecule to cross the glomerular ultrafiltration barrier, both electrostatic and steric hindrance must be considered. In relative terms, electrostatic factors probably play a lesser role in determining the transglomerular passage of the smallest macromolecules. Electrical charge probably assumes greater importance as the effective radius of the macromolecule approaches the diameter of the theoretical "pore." The magnitude

of relative interplay between electrical charge versus molecular size and shape as determinants of transglomerular passage has not yet been established for any significant number of plasma proteins.

Hemodynamic factors. In addition to physicochemical considerations, renal hemodynamic alterations provide other major influences on the transglomerular passage of macromolecules [20]. The mechanisms whereby hemodynamic changes affect urine protein excretion, however, are not well understood. One must remember that convective and diffusive forces are important theoretical determinants of macromolecular transport across the capillary wall, and that these forces are also influenced by glomerular hemodynamics. Administration of vasoactive compounds such as angiotensin [25, 26] and norepinephrine [27], assumption of the upright posture [28, 29], and exercise [4] all can lead to increased urine protein excretion. Proteinuria in these settings has been attributed to a function of the reduced renal blood flow and altered glomerular hemodynamics. Local increases in protein concentration along the glomerular capillaries (when glomerular plasma flow is reduced and filtration rate is relatively well maintained), increases in the permeability of the limiting glomerular membrane or its surface area available for transport, and increases in transglomerular pressure might be some of the mechanisms responsible.

Mechanisms of abnormal proteinuria

The major mechanisms whereby increased amounts of protein appear in the urine are: *(1)* elevated plasma concentrations of normal or abnormal proteins ("overflow" proteinuria such as lysozymuria in leukemia or Bence-Jones proteinuria [30]; *(2)* direct addition of proteins to tubular fluid by the renal tubular epithelium (Tamm-Horsfall proteinuria) [31, 32]; *(3)* altered renal tubular reabsorption of normal amounts of filtered proteins [33-36]; and *(4)* an altered capillary wall with a resultant increase in permeability secondary to a loss of glomerular polyanions or other causes of decreased permselectivity [9]. Whatever the cause of abnormal proteinuria, its magnitude can be increased by the same renal hemodynamic changes that are capable of increasing protein excretion by the healthy kidney. Little is known about the relative contribution of these mechanisms to the genesis of "isolated" proteinuria in asymptomatic patients. In view of the undoubted heterogeneity of the patient population with this syndrome, we logically can suspect that any of the possible mechanisms might be operative in a given patient at a given time.

Against this background, let us turn to a detailed consideration of the clinical significance and, when possible, the mechanisms of isolated proteinuria in asymptomatic and apparently healthy patients.

Clinical significance of proteinuria in apparently healthy patients

Uncertainty still surrounds the clinical significance of "isolated" proteinuria. Several factors are responsible for this state of affairs. First, it has long been known that qualitative proteinuria occurs both in the presence and absence of underlying histologic alterations of renal structure [37-47]. Second, although progressive renal disease appears subsequently in some patients [37, 48-49], one study has shown that the incidence of proteinuria in young adults is greater than the incidence of subsequent death from renal failure [50]. This finding strongly suggests that kidney disease might not exist in many such patients or that if it does, it does not cause death from renal failure. Third, we must recognize that conclusions derived from a study of one population are not necessarily applicable to another group. Finally, a profuse array of descriptive terms has been applied frequently to proteinuria observed in apparently healthy patients; juvenile, physiologic, orthostatic, constant, persistent, cyclic, intermittent, isolated, benign, minimal, and transient comprise only a partial list of the descriptive terms. In many instances, these terms have not been defined clearly; in others, the use of differing criteria has complicated the comparison of results between studies.

For these reasons, the exact definition of the clinical characteristics of the proteinuric population under consideration is of great importance. The remainder of the present discussion will focus exclusively on the clinical significance of proteinuria in a single, large, and arbitrarily defined adult population of patients in whom proteinuria is always first observed as an "isolated" clinical finding. It will apply only to patients who are asymptomatic and seemingly healthy at the time of initial examination, and who exhibit no evidence of systemic disease, impaired renal function, or *any* abnormality of the urine sediment. Excretory urography and nuclear or ultrasonic imaging are always within normal limits, and the patients have no history of kidney or genitourinary tract disease. In such patients, proteinuria is often first detected during a routine physical examination, perhaps in preparation for entrance into military service, participation in an athletic program, or application for life insurance or

employment. Daily total protein excretion is usually, but not necessarily, less than 1.0 g. Most patients thus far described have been relatively young adults at the time of initial clinical presentation, but this fact might be related to the paucity of comparable survey observations in older populations. Neither the incidence nor prevalence of proteinuria as an isolated finding among various age or population groups is certain. Estimates of the incidence of qualitative proteinuria during casual or routine urinalysis in military inductees and other adult populations have varied widely, ranging from values of 0.6% to 8.8% [51–54].

Classification of isolated proteinuria. What methods should one use in assessing the clinical significance of isolated proteinuria in an individual patient? In general, proteinuria has been classified according to two clinical approaches, one without regard to body posture, and the other taking body posture into account. Using the first approach, the pattern of protein excretion on repeated qualitative testing is designated "transient" or "intermittent" if proteinuria comes and goes, and "persistent" if proteinuria is found on analysis of all specimens. In the second approach, "serial urine collection tests" identify proteinuria as "constant" if it is present both during recumbency and during quiet upright ambulation, "fixed and orthostatic" if it is present consistently only in the upright posture, and "transient" or "intermittent" and "orthostatic" when it is present inconsistently only in the upright posture [55, 56]. Multiple urinalyses must be performed at the time of initial examination to identify the pattern correctly. The significance of many of these arbitrarily classified types is not certain: the various types probably should be viewed not as specific clinical entities, but as consequences of diverse causes and mechanisms. Further, even the relationship between persistent and constant proteinuria, as just defined, has not been delineated clearly. Although it seems likely that patients with these patterns are drawn from similar populations, studies using both approaches, that is, with and without regard to posture, have not been performed in the same individuals. I would now like to discuss these two different approaches to the investigation and classification of isolated proteinuria.

Classification according to repetitive urinalysis without control of body posture. As noted above, at least two distinct qualitative patterns of isolated proteinuria emerge when routine urinalyses are carried out repetitively over a short period: the persistent presence of qualitative proteinuria, or the intermittent or transient presence of qualitative proteinuria. Several years ago, Levitt performed a retrospective study to establish the clinical significance of these types of proteinuria [50]. The study group comprised graduates of the University of Minnesota who were given repetitive urinalyses on entrance to the university in 1925; each had qualitative proteinuria. By 1966, 41 years later, the mortality rate of this group was compared with that of presumably healthy 18-year-olds who had undergone examinations for life insurance in 1925, and whose urinalyses revealed no proteinuria qualitatively. The mortality rate was significantly higher in the patients who had had qualitative proteinuria in more than 80% of their initial urinalyses, that is, those with persistent proteinuria. In contrast, no difference in mortality rate was noted in the patients who had had proteinuria in less than 50% of their initial specimens, that is, those with intermittent or transient proteinuria. These findings imply that the long-term outlook is worse when repetitive examination reveals persistent proteinuria.

In France, Antoine et al studied 16 patients in whom persistent proteinuria was an isolated finding [37]. Percutaneous renal biopsy revealed a heterogeneous spectrum of morphologic alterations in 12 of the 16 patients. Nevertheless, only 2 of these patients developed renal insufficiency after follow-up periods ranging from 8 to 28 years. The authors concluded that even in patients with documented renal pathology, the progression to renal failure is remarkably indolent. Included in Antoine's study were 10 other patients with the same clinical and histologic findings as the 16 patients described above, but these 10 also had microscopic hematuria. This single additional indicator of disease activity was attended by more rapid progression of renal functional impairment.

Classification according to repetitive urinalysis with control of body posture. For many years we have used a simple serial urine collection test to relate the qualitative appearance of proteinuria to changes of body posture [55, 56]. When the test is conducted during moderate antidiuresis, results are reproducible in the same patient over short periods of time. On the morning after overnight fluid deprivation, two or more urine samples are collected consecutively during each of two sequentially assumed body postures: recumbency and quiet upright ambulation. Artificial upright lordosis is not induced. A qualitative test for protein (10% sulfosalicylic acid) and a measurement of urine osmolality are performed on each urine sample.

As noted previously, one of three qualitative patterns emerges in an individual patient. Constant proteinuria occurs in approximately 5% to 10% of young men with proteinuria on routine urinalysis

where posture is not controlled [56]. Fixed and reproducible orthostatic proteinuria occurs in approximately 15% to 20% of young men whose proteinuria is detected initially on routine urinalysis [56]. As I mentioned earlier, this type of proteinuria was initially exhibited by the patient under discussion today. Transient orthostatic proteinuria is claimed by King to be the most common of the three posturally defined patterns, perhaps occurring in 70% to 75% of young men with isolated proteinuria on routine urinalysis [56]. Unfortunately, transient orthostatic proteinuria has been studied far less thoroughly than have either fixed and reproducible orthostatic proteinuria or constant proteinuria. Approximate incidence figures for these types of proteinuria are available only for young men; similar figures are not available for women or other age groups.

Quantitative measurements of total protein excretion have been carried out in patients who have clear evidence of constant proteinuria and fixed and reproducible orthostatic proteinuria. Values for total protein excretion are often higher even during recumbency in patients with fixed and reproducible orthostatic proteinuria than in healthy patients whose qualitative tests are negative for protein in both the recumbent and upright postures [28, 29]. But the amount of protein excreted is not sufficiently high to permit detection with the usual qualitative tests. The significance of this finding has not been established, nor is its occurrence known to be universal in patients with a qualitative pattern of orthostatic proteinuria other than that termed fixed and reproducible. Indeed, quantitative protein excretion during recumbency might well be within normal limits in patients with transient orthostatic proteinuria [57].

(A) "Constant" proteinuria. For many years "constant" proteinuria, even as an isolated finding, has been regarded as *prima facie* evidence of kidney disease. Definite morphologic evidence of diverse forms of kidney disease is found by renal biopsy in most instances. Most of these patients probably have proteinuria that is persistent on repetitive routine urinalysis without postural control. In view of the marked diversity of the underlying renal pathology, it is illogical to expect that all such patients will follow an identical clinical course. Nevertheless, the clinical course of constant proteinuria is remarkably indolent in the absence of other indicators of active disease such as microscopic hematuria. Although few long-term follow-up studies of patients with constant proteinuria have been performed, the results of one study demonstrated that approximately 80% of such patients still exhibited constant proteinuria after an average 6-year period. Of these, the majority had developed abnormal urine sediment, and almost 50% had developed mild hypertension, but very few had developed renal insufficiency [48, 49].

(B) Orthostatic proteinuria. The exact clinical significance of islolated orthostatic proteinuria remains controversial. In contrast to constant proteinuria, orthostatic proteinuria has been regarded as a benign and transient condition not associated with underlying kidney disease [58–60]. This concept of the disorder might be true in many patients, particularly in children. Other observations, however, have suggested that orthostatic proteinuria might be a reflection of incipient kidney disease, at least in some patients [49, 61]. This controversy cannot be resolved until complex clinical and physiologic issues are clarified. To shed some light on the significance of orthostatic proteinuria, I would now like to examine the renal biopsy findings in these patients, the possible mechanisms involved in the proteinuria, and our long-term prospective studies.

Light-microscopic studies of kidney biopsy specimens from young adult males with fixed and reproducible orthostatic proteinuria revealed that 8% had unequivocal evidence of renal disease, 45% had subtle but definite alterations of glomerular structure (segmental or generalized capillary wall thickening without alteration of the basement membrane, or focal and segmental hypercellularity), and 47% exhibited a histologic pattern that appeared normal [45]. A limited number of electron-microscopic observations have confirmed a subtle form of segmental and focal glomerular alterations [46, 62], and immunohistologic studies have shown that both immunoglobulin and complement are localized within such foci [63]. Recent histologic observations in patients with intermittent orthostatic proteinuria demonstrate minimal changes without immunoprotein on immunofluorescent microscopy, but only a small number of such patients have been studied [47].

The mechanism by which assumption of the quiet upright posture effects increased protein excretion is still uncertain. Regardless of the exact nature of the glomerular changes just described, their existence provides one possible explanation for the proteinuria, that is, an underlying capillary wall defect, which facilitates an increased transglomerular passage of plasma proteins. By itself, however, the existence of an altered capillary wall does not explain abnormal protein excretion occurring only during quiet upright ambulation [57]. Earlier researchers

postulated that any one of the several renal hemodynamic adjustments to standing might serve as the primary cause of orthostatic proteinuria; renal venous congestion or ischemia and a reduction of filtration rate all have been implicated [58, 64]. This hypothesis became suspect when it was shown that the upright renal hemodynamic response was no different in patients with fixed orthostatic proteinuria than it was in normal subjects [20, 65]. A quantitatively similar reduction of renal plasma flow and filtration rate, and an elevation of filtration fraction were observed in both groups. Of these three possible hemodynamic determinants of transglomerular protein transfer, the results of clearance studies [28] indicated to us that the normal reduction of plasma flow was of greatest importance. For example, experimentally induced renal vasodilation that obliterated the usual reduction of renal plasma flow was accompanied by a strikingly smaller rise of protein excretion than usual. We suggested that some function of the reduction of renal blood or plasma flow might secondarily permit an increased protein transfer across an altered capillary wall. According to this view, the combination of an altered capillary wall and the normal reduction of renal blood flow in the upright posture might be sufficient to effect an increased transglomerular passage of protein that readily exceeds the normal tubular reabsorptive capacity. One can speculate that the secondary hemodynamic contribution to fixed orthostatic proteinuria might be similar to that occurring during the administration of angiotensin in experimental animals [25, 26]. This hypothesis is tentative and other possibilities exist. For example, an upright alteration of renal tubular reabsorption of protein has not yet been excluded. Alternatively, increased capillary permeability to plasma proteins during standing might be mediated via a direct effect of certain humoral agents on an altered capillary wall, agents whose release is also increased by postural changes. Such a role has been suggested for renin, angiotensin, and circulating vasoactive amines because of their capacity to produce proteinuria in animals [25–27, 66, 67].

Whatever the role of the alterations of glomerular structure in the pathogenesis of fixed and reproducible orthostatic proteinuria, only long-term prospective studies can determine their clinical significance. Our own 10-year follow-up study of young men with an initial diagnosis of fixed orthostatic proteinuria demonstrated that 49% still exhibited qualitative proteinuria [61]. No evidence of renal functional impairment or progressive renal disease had appeared in any of the patients, including the patient presented today. Furthermore, no relationship existed between the initial renal histology and the subsequent pattern of renal function of proteinuria. In short, the 10-year prognosis of young men with fixed and reproducible orthostatic proteinuria is excellent. A similarly benign intermediate-term course of 5 to 10 years has been described by other observers [67–69].

The significance of the subtle glomerular alterations that we found in 45% of our patients is uncertain, but the decreasing frequency of proteinuria and the preservation of normal renal function in this group suggests that the glomerular findings are not a manifestation of progressive renal disease. Until more time elapses, however, we cannot exclude the possibility that renal function will deteriorate in the patients who still had proteinuria when studied 10 years after the initial evaluation. As I mentioned previously, these results are not surprising in view of the heterogeneity of the histologic alterations.

Taken together, these findings suggest that fixed and reproducible orthostatic proteinuria does not necessarily represent a transient condition of adolescence—in some patients it might reflect the earliest expression of future renal disease. Continued observation is necessary to establish the validity of this hypothesis. In fact, our patient today is one whose return visit in 1979 was occasioned by his willingness to participate in the 20-year follow-up study of our original group of patients. Obviously, he has continued to do well. Because his proteinuria is now transient and his renal function has remained normal, I strongly suspect that his long-term prognosis is excellent. Our 20-year follow-up study, in cooperation with Drs. P. Springberg and L. Garrett at Wilford Hall USAF Medical Center and Dr. A. L. Thompson at the University of Nevada Medical Center, is just now underway so our observations are only preliminary. We have, however, reexamined 18 of the original 64 patients, and to date none has developed renal insufficiency. We hope the number of participants in the 20-year follow-up study will be large enough to permit meaningful comparisons with the earlier follow-up examinations [61].

Virtually no long-term data are available in patients with transient orthostatic proteinuria, but most clinicians believe that the prognosis of patients with this finding is excellent [50]. In many such patients, transient episodes of orthostatic proteinuria might reflect nothing more than fever, exercise, or exposure to environmental factors such as heat or cold. Indeed, as in angiotensin-induced proteinuria in the rat, this form of upright proteinuria

might reflect nothing more than a transient and exaggerated renal hemodynamic response to these or other stimuli.

Summary of renal structural alterations in patients with "isolated" proteinuria

Renal biopsy specimens have been examined from patients in the five descriptive categories of isolated proteinuria I have used: persistent or intermittent proteinuria (defined on sequential routine urinalysis without control of body posture) [37, 40, 41]; constant proteinuria during both recumbent and upright postures [43]; and transient [47] or fixed and reproducible orthostatic proteinuria as defined during appropriate postural maneuvers [43, 45]. In four of the five categories examined so far, a varying but important incidence of "definite" histologic alterations has been reported (about 10% to 70%), all of which have been sufficiently distinct to warrant a firm histologic diagnosis of renal disease ("definite" histologic alterations have not yet been reported in patients with transient orthostatic proteinuria). The lesions themselves have been extremely heterogeneous, and a consistent relationship has not been observed. The incidence of definite renal pathology has been found to be similarly high (about 40% to 70%) in patients with persistent, intermittent, or constant proteinuria [37, 40, 43, 70], whereas a much lower figure (about 10%) has been found in patients with fixed orthostatic proteinuria [45]. In other patients from all five of the groups, the incidence of disparate but minimal alterations has been similarly variable (about 10% to 70%). In still others, perhaps most frequently in patients with transient or fixed orthostatic proteinuria, the renal architecture has appeared entirely normal on light microscopy [45, 47], although subtle architectural "defects" of the glomerulus have been described on electron microscopy in a few patients [46, 61]. It seems safe to conclude that, with the possible exception of transient orthostatic proteinuria, (*1*) each of these five types of proteinuria is associated with a broad spectrum of histologic findings ranging from normal renal architecture to definite evidence of disease; (*2*) a similarly heterogeneous display of underlying renal pathology or architectural alteration occurs in each type but the frequency of definite disease is lowest by far in patients with transient or fixed orthostatic proteinuria; and (*3*) no absolute relationship exists between the type of proteinuria and the presence or absence of renal pathology. Renal biopsy remains the only means of distinguishing between the patient with structural renal disease and the one without.

Unfortunately, the description of definite pathologic alterations per se does not provide any necessary insight into their actual clinical significance as a cause of subsequent morbidity or mortality. One still must determine whether a particular lesion is static, resolving, or progressing. Prospective studies are clearly required. We also must continue our search for functional indexes of disease activity as an aid to determining the activity of the pathologic lesions.

In our approach to the management of patients with isolated proteinuria, we emphasize yearly follow-up evaluation. The initial evaluation includes a thorough physical examination, a determination of the persistence of a given qualitative pattern, urinalysis, and measurements of quantitative protein excretion and endogenous creatinine clearance. Ultrasonography is sometimes performed as well. Renal biopsy usually is not undertaken unless there is a distinct change in the clinical course, such as an abrupt and definite increase in daily protein excretion, the appearance of distinct and persistent abnormalities of the urine sediment, or impairment of renal function.

It is interesting to speculate that a persisting pattern of qualitative proteinuria over several years—whether it be persistent, intermittent, fixed, or transient orthostatic or constant in type—might be attended by an important incidence of underlying renal pathology [41–46, 50, 51]. In fact, it would not be surprising to observe in the same patient at different times over a relatively long period different types of proteinuria, because its detection depends on the simultaneous interaction of many variables (for example, posture, urine concentration, and the

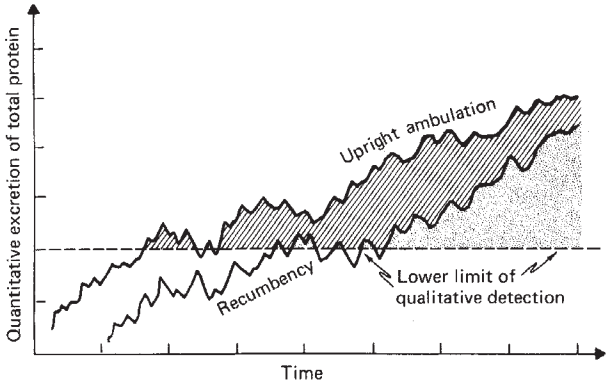


Fig. 1. *Sequential relationship between quantitative protein excretion and qualitative tests for urine protein in a hypothetical patient with progressive renal disease (Reprinted with permission from S. Karger* [71]).

natural history of an underlying disease process) [71]. Figure 1 depicts a hypothetical patient whose disease progression is accompanied by a variable but steady increase of total protein excretion during both recumbency and upright ambulation. Depending on the relationship between the lower limits of qualitative urine protein detection and the changing influences on urine protein excretion, an ever-changing pattern of qualitative proteinuria will emerge. At various times, a patient might exhibit intermittent or transient orthostatic proteinuria, or perhaps it might seem to become fixed for a variable period [71]. Eventually, quantitative protein excretion might rise sufficiently to permit its qualitative detection in both recumbent and upright specimens, that is, the proteinuria becomes constant. Some patients move through this sequence so explosively that constant proteinuria seems to exist from the very onset of disease. In others, the disease progresses so slowly that a variable but generally orthostatic pattern is observed for years. Eventually, if the underlying disease progresses sufficiently, protein excretion can rise during recumbency and yield the pattern of constant proteinuria; alternatively, the disease process can heal, and proteinuria disappears completely. Considerations such as these should underscore the difficulties that beset any attempt to relate a given clinical observation to any particular pattern of qualitative proteinuria. Nevertheless, although the long-term prognosis still must be regarded with reservation, if persistent proteinuria is the *sole* alteration, the 10-year outlook is excellent in most patients, as in the patient presented today.

Questions and answers

DR. JEROME P. KASSIRER: Our approach to the diagnosis of orthostatic proteinuria has been to measure protein excretion using a quantitative sulfosalicylic acid method during 8 hours of recumbency and again during 16 hours of routine activities in the upright posture. Using this method we have diagnosed orthostatic proteinuria when protein excretion is abnormal only in the upright posture. Do you think there is any advantage to this quantitative approach over the qualitative method you used?

DR. ROBINSON: I don't know. Unfortunately, too few descriptions have been published about the relationship between recumbent and upright quantitative values for total urinary protein excretion and the qualitative patterns I have described. At least in patients with fixed orthostatic proteinuria, however, quantitative excretion seems usually to be increased during recumbency, but the protein excretion does not rise sufficiently to permit qualitative detection. I cannot say whether that is the case in transient or intermittent proteinuria. Resolution of the question also depends on the sensitivity of our methods for quantifying small amounts of proteinuria and the adequacy of our definition of the "normal" range of protein excretion in the recumbent posture.

DR. KASSIRER: We occasionally observe patients who, in the course of recovering from the nephrotic syndrome or poststreptococcal nephritis, show an orthostatic pattern of protein excretion. These patients seem to have a benign long-term prognosis. Is there any solid evidence to support this contention?

DR. ROBINSON: I don't know the answer to that question either. I know of no solid data that relate prognosis in those disorders to the presence or absence of orthostatic proteinuria at some time during the clinical course.

DR. CECIL H. COGGINS (*Acting Chief, Renal Unit, Massachusetts General Hospital, Boston*): In reviewing the literature on patients with mild to moderate proteinuria, I cannot find very much good data correlating the clinical information with sophisticated histologic analysis. In a few surveys, patients were biopsied but not followed, and even in these studies the biopsies usually were not examined by electron microscopy or immunofluorescence. I believe that you and your colleagues have carried out the few studies that do correlate reliable clinical information with solid pathologic analysis.

DR. ROBINSON: Thank you, Dr. Coggins. I agree that there are too few prospective followup studies. Parenthetically, insofar as our own studies are concerned, most of the paraffin blocks containing the original biopsy specimens are still available. In the near future, I hope that we can reexamine new sections from these blocks for comparison with those cut originally. It will be interesting to note the similarity or lack thereof between our original morphologic interpretations and those made independently 20 years later.

DR. JORDAN J. COHEN: Let us assume that your reexamination of the original biopsy material confirms your initial impression that asymptomatic patients with mild proteinuria often have detectable histologic changes. To interpret such a finding, one would have to know the spectrum of histologic findings in truly normal persons without proteinuria. Are sufficient histologic data available to define what the normal spectrum is?

DR. ROBINSON: I think we have a far better understanding today than we did in 1958 to 1960. For instance, kidney biopsies performed one hour after renal transplantation in well-matched siblings offer one basis for comparison. Nevertheless, determining a precise definition of normal can be a very difficult task.

DR. KENNETH SHAPIRO (*Renal Fellow, NEMCH*): You alluded to the possible role of angiotensin in the pathogenesis of postural proteinuria. Are you aware of any studies using angiotensin blockers or indomethacin to treat this condition?

DR. ROBINSON: No, there are none to my knowledge.

DR. JOHN T. HARRINGTON: Dr. Robinson, your studies on postural proteinuria have given us a great deal of insight into the significance of proteinuria of less than 1 g/day. Dr. Coggins recently published the first full results of the Adult Idiopathic Nephrotic Syndrome Collaborative Study analyzing patients with proteinuria greater than 3.5 g/day [72]. I am interested in your thoughts regarding the group in the middle, that is, those who excrete 1 to 3 g of protein per day.

DR. ROBINSON: In general, it is my bias that the greater the degree of proteinuria, the higher the likelihood of underlying kidney disease. Depending on the results of the urine sediment examination, I might wish to further test a patient who excretes 1 to 3 g of urinary protein per day. Some clinicians would say that renal biopsy should be performed if the excretion rate is greater than 2.0 g/day. If proteinuria of such magnitude is an isolated finding, I believe that one can postpone biopsy until the first appearance of a change in clinical status. Overall, I suspect that the subsequent appearance of such changes will be much more frequent and earlier than it is in patients with lesser degrees of proteinuria. A good study of these patients, which correlates long-term clinical information with modern renal pathology, is needed.

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