FIXED AND REPRODUCIBLE ORTHOSTATIC PROTEINURIA

I. Light Microscopic Studies of the Kidney

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Considerable disagreement still exists as to the exact etiology and clinical significance of orthostatic proteinuria in asymptomatic patients. Traditionally, it has been regarded as a benign and transient condition, most common during adolescence, and unassociated with underlying renal disease.[1-6] However, recent clinical studies have suggested that this condition is not always transitory in nature and that the incidence of associated renal disease is much higher than commonly supposed.[7-8] Clarification of these widely divergent points of view is of special importance to the military services in order that individuals with orthostatic proteinuria may be utilized both justly and properly.

Although there have been innumerable reports on various clinical aspects of orthostatic proteinuria, no detailed articles dealing with histologic studies of the kidney have yet appeared. We have recently completed an investigation of renal biopsy material obtained from 56 asymptomatic patients with "fixed and reproducible" orthostatic proteinuria. Our object was to determine whether diffuse forms of renal disease or other architectural defects could be found which might be related to this particular disorder.

Material and Methods

Between June, 1959, and June, 1960, 366 asymptomatic basic military trainees with proteinuria at the time of enlistment were referred to our clinic for evaluation. These individuals had been permitted to enter military service only because their examining physicians had felt that the proteinuria was "orthostatic" or "transient" in nature. Routine urinalyses confirmed the presence of proteinuria in 189 individuals.

This investigation was supported, in part, by Research Contract 41(657)-368 with the School of Aviation Medicine, USAF Aerospace Medical Center (ATC), Brooks Air Force Base, Texas.

Accepted for publication, May 2, 1961.

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Ninety-two patients with reconfirmed proteinuria were selected for hospital admission and more thorough study.

All hospitalized patients were placed on a special ward with personnel intimately familiar with the details of the investigation. Particular attention was paid to the proper classification of urinary protein excretion patterns. Patients with "fixed and reproducible" orthostatic proteinuria were identified according to the results of a rigidly supervised serial urine collection test as described below:

1. Dry supper at 6:00 p.m. on the evening preceding the test. No fluids were allowed until 8:00 a.m. the following morning.

2. Patients remained recumbent in bed from 8:00 p.m. until 8:00 a.m. A recumbent voided urine specimen was obtained at 10:00 p.m. and discarded.

3. Urine voided during recumbency was again collected at 6:00 and 8:00 a.m. Both samples were saved for analysis.

4. Light ambulatory activity about the ward was required from 8:00 a.m. until completion of the test at 3:00 p.m. Fluids were limited to 500 ml. during this period.

5. While the patients were upright, voided urine specimens were obtained at 10:00 and 11:00 a.m., 12:00 noon, 2:00 and 3:00 p.m., and saved for analysis.

A qualitative test for protein and an estimate of specific gravity were obtained on each urine specimen saved for analysis. A sample was considered free of protein when tests for protein were negative and its specific gravity was 1.018 or higher.

This procedure has been found to be a reliable clinical means of relating the appearance of proteinuria to changes of body posture.[8-9] Urinary protein excretion patterns were classified according to the criteria of King[8] after the results of at least 3 consecutive tests were available. In brief, proteinuria was termed "persistent" if detected in both the recumbent and upright postures, and "orthostatic" if found only during standing. Two types of orthostatic patterns were recognized: (a) one in which upright proteinuria was repetitively and consistently demonstrated by serial testing; and (b) another in which upright proteinuria was variable and inconstant in its appearance and not demonstrated consistently from day to day. The first type of orthostatic pattern was termed "fixed and reproducible"; the second was referred to as "transient" in nature. Patients with previously documented proteinuria whose serial collection tests were negative repeatedly for protein were presumptively included in the "transient" group.

According to the results of this test, 64 patients had "fixed and reproducible" orthostatic proteinuria. Our observations were limited solely to this group of patients. All subjects were asymptomatic and apparently healthy young men whose ages ranged between 17 and 24 years (average, 19 years). In each of 3 patients an equivocal history of previous renal disease was elicited. Excretory urograms and conventional clinical estimates of renal function were within normal limits in all. Subtle abnormalities of the urinary sediment were noted on extremely rare occasions.

Percutaneous renal biopsy was performed according to the technique described previously by Muehrcke, Kark, and Pirani.[10] However, the left kidney instead of the right was selected for biopsy purposes. No adverse complications were encountered.

Tissue sections from all patients were examined by conventional light microscopic techniques. Electron microscopic studies were made of 6 specimens and will be reported in detail in a subsequent communication.[11] In preparation for light microscopy, biopsy material was fixed in 10 per cent neutral buffered formalin in saline. After fixation, the tissue was embedded in paraffin and sections were cut as thinly as possible with a conventional microtome. Paraffin preparations were stained with hematoxylin and eosin and by the periodic acid-Schiff (PAS) method. Samples were considered adequate for recognition of diffuse renal lesions if 5 or more glomeruli were included.

Biopsy specimens containing minimal and subtle histologic alterations were eval-

uated with considerable conservatism and with due regard for such factors as section thickness, which might erroneously affect interpretations. Moderate reliance was placed upon the comparison of such specimens with those which we were fortunate to obtain from 4 healthy young male volunteers (average age, 22 years) without proteinuria or evidence of renal disease. All slides were intermixed and reviewed independently by two examiners. Agreement was usually excellent. When agreement could not be reached, the changes in question were listed as doubtful or equivocal.

RESULTS

Fifty-eight percutaneous renal biopsy specimens were obtained from 56 patients with fixed and reproducible orthostatic proteinuria. Fifty-one specimens (88 per cent) exhibited 5 or more glomeruli (average, 17) and were regarded as adequate in size for diagnostic purposes. These 51 biopsies form the basis for the present report.

The character and frequency of the various structural alterations observed are listed in Table I. For convenience and ease of presentation, specific alterations of the major histologic divisions of the kidney will be described separately.

Glomerulus

The main features of normal glomerular architecture are well established. The type of capillary wall structure illustrated in Figures 1 and 2 is typical of that seen in hematoxylin and eosin stained preparations from normal volunteer subjects. The delicacy and thinness of the peripheral capillary loops is of particular note.

In specimens from patients with orthostatic proteinuria, one of the most consistent and interesting alterations was exhibited by the filtration surfaces of the glomerular capillary loops. Twenty-two (43 per cent) of 51 adequate specimens revealed definite minimal to moderate thickening of the glomerular capillary wall (Figs. 3, 4, and 15). In an additional 7 cases (14 per cent) suggestive changes of this type were demonstrated. The glomerular capillary walls of the 22 remaining specimens were identical to those observed in normal subjects of the same age group.

It should be emphasized that capillary wall thickening was often of minimal intensity and subtle in its appearance. It was most easily and reliably detected among the peripheral capillary loops of the tuft. Involved capillary walls often appeared stiffened and devoid of their normal resiliency (Fig. 5). The cross-sectional area of the capillary lumens was affected in a variable manner. In most sections, capillary patency appeared compromised and reduced by the thickened walls (Figs. 6 and 7). Areas containing dilated and uninvolved capillaries were often noted adjacent to the foci with decreased capillary patency. On the other hand, focal areas with widely patent but thickened capillary loops were also noted within some glomeruli in 11 specimens (Figs. 5 and 15).

Capillary wall thickening was variably distributed throughout the glomerular population of individual samples. The majority of the glomeruli were either diffusely or focally affected in 15 cases. The remaining 7 cases showed either focal or diffuse capillary wall thickening of less than half of the glomerular sample (Table I). Capillary wall thickening was relatively severe in only 5 of the 22 specimens. It was sufficiently

TABLE I

STRUCTURAL ALTERATIONS OF THE KIDNEY IN FIXED AND REPRODUCIBLE ORTHOSTATIC PROTEINURIA *

Type of alteration	Biopsy specimens	
	No.	Per cent
Glomerulus		
Capillary wall thickening, definite	22	43
Diffuse involvement of > 50% of glomeruli	10	
Focal involvement of > 50% of glomeruli	5	
Diffuse involvement of < 50% of glomeruli	1	
Focal involvement of < 50% of glomeruli	6	
Capillary wall thickening, questionable	7	14
Basement membrane thickening, PAS-positive	5	10
Hypercellularity	21	41
Diffuse involvement of > 50% of glomeruli	4	
Focal involvement of > 50% of glomeruli	2	
Diffuse involvement of < 50% of glomeruli	5	
Focal involvement of < 50% of glomeruli	10	
Eosinophilic granules within capsular space	34	67
Tuft enlargement	21	41
Capillary dilatation, focal	11	22
Congestion, focal	5	10
Ischemia, focal	9	18
Capsular adhesions, definite	5	10
Hyalinized and fibrotic glomeruli	3	6
Capillary "occlusion" with eosinophilic material	3	6
Capsule		
Thickening	11	22
Proliferation, minimal	16	31
Interstitial Tissue		
Fibrosis, focal	11	22
Inflammation, focal	4	8
Edema, focal	3	6
Tubules		
Atrophy, focal	11	22
Dilatation, focal	1	2
Cell casts, intraluminal	10	20
Eosinophilic granules, intraluminal	31	61
Other		
Arteriolar thickening	1	2

* From 51 adequate renal specimens.

advanced in 3 to warrant an emphatic diagnosis of diffuse membranous glomerulonephritis (Fig. 7). Differences between minimal and presumably early thickening and the most advanced variety are contrasted in Figures 3 and 7.

In most cases we were unable to determine precisely which components of the capillary wall were responsible for the increase in thickness. Basement membrane thickening was noted in PAS preparations of the 5 specimens with most advanced changes (Fig. 9) and probably contributed to the thickened appearance of the capillary wall in these samples. Early and minimal focal condensations of basement membrane substance were sometimes noted in other cases (Fig. 8), but the basement membrane structure of the capillary loops was usually normal and intact.

Twenty-one biopsy specimens (41 per cent) revealed glomerular hypercellularity of varying degree. In all but 4, hypercellularity was associated with capillary wall thickening. Although diffuse hypercellularity of individual glomeruli was noted occasionally, it was most often focal in nature. Over half of the glomerular population was focally or diffusely hypercellular in only 6 specimens. Focal areas of glomerular hypercellularity were manifest as compact collections of nuclei which were best seen at the periphery of the glomerular tuft (Figs. 4, 7, 10 and 11). These nuclei were felt to be epithelial in character although light microscopy did not always permit precise classification. Epithelial cells in general often appeared enlarged and contained an abundance of cytoplasm (Fig. 12). In the main, the degree of focal hypercellularity seemed to parallel the extent of the capillary wall thickening. Glomerular tufts were increased in size in over half of the cases with well defined capillary wall thickening. The capsular space was almost completely obliterated in many instances (Figs. 6, 7, and 13). Hypercellularity, capillary wall thickening, and focal capillary dilatation appeared to be important causes of this tuft enlargement.

Another frequent feature (34 of 51 specimens) was tiny clusters of small, brightly eosinophilic granules within the capsular space; these were very faintly PAS-positive (Fig. 14). They were variably sized and were always seen in close proximity to the epithelial periphery of the glomerular tuft and appeared to have arisen from the epithelial cytoplasm of the capillary loops. They were not observed with certainty in samples from normal volunteers, and had to be carefully distinguished from smaller and less eosinophilic granular debris of tubular origin which occasionally extruded into the capsular space.

Other alterations of glomerular architecture were felt to be of doubtful significance. In many hematoxylin and eosin-stained preparations, fibrinous adhesion-like strands of lightly eosinophilic material appeared to attach an occasional glomerular tuft to the adjacent capsular epithelium (Figs. 13 and 15). However, definite PAS-positive glomerulocapsular adhesions were observed in only 5 specimens. Collections of a

moderately eosinophilic and finely granular substance of unknown composition seemed to occlude the capillary lumens of occasional glomerular tufts in 3 cases. Focal areas of glomerular congestion or ischemia were sometimes seen (10 and 18 per cent, respectively). Lastly, hyalinized glomeruli were noted sporadically in 3 additional cases. Two of these exhibited clear evidence of either membranous glomerulonephritis or pyelonephritis.

Bowman's Capsule

Early thickening of the capsule wall and minimal nuclear proliferation of the capsular epithelium were apparent in 22 and 31 per cent, respectively, of adequate specimens (Table I). Most sections with early capsular thickening (Fig. 13) also revealed glomerular capillary wall thickening. Capsular thickening and periglomerular fibrosis were surrounded by small foci of active inflammation in 3 samples (Fig. 16). Nuclear proliferation of the capsular epithelium was always of slight degree and did not appear related to the occurrence of other alterations.

Interstitial Tissue

Small foci of cortical interstitial fibrosis and tubular atrophy were seen in 11 cases. In 4 instances, a modest degree of inflammatory reaction could be seen about the periphery of these areas. However, only 1 specimen revealed sufficient inflammatory change to merit a diagnosis of active pyelonephritis (Fig. 16).

Tubules

The cortical and medullary tubular epithelium appeared unaltered in most cases. Of interest, however, was the observation that 61 per cent of the biopsy specimens revealed small granules within the proximal tubular lumens; these possessed the same tinctorial properties and physical appearance as those previously described within the capsular space. Definite intracytoplasmic accumulation of these granules within tubular epithelium was not observed. Similar granules were observed with rarity in the tubular lumens in normal volunteers.

Small focal areas of cortical tubular atrophy and interstitial fibrosis were noted in 11 cases. Focal tubular dilatation was found on only one occasion.

Discussion

These observations indicate that fixed and reproducible orthostatic proteinuria is frequently associated with underlying morphologic alterations of the kidney. Two important factors must be kept in mind as the

possible significance of these findings is discussed. First, since the case material was obtained from a strictly defined population group, the findings are not necessarily representative of all persons with this form of proteinuria regardless of age. Second, it should be re-emphasized that this study was confined solely to patients whose orthostatic proteinuria was fixed and reproducible. Differentiation of this type of proteinuria from that of a "transient" nature is of particular importance. Transient orthostatic proteinuria is seen much more often, the fixed and reproducible variety accounting for only about 15 per cent of all cases of asymptomatic proteinuria.[8] Such distinctions must be clearly recognized since these two forms of orthostatic proteinuria may well provide entirely different etiologic and prognostic implications.

For purposes of discussion, all biopsy specimens were divided loosely into 3 broad groups. Although somewhat artificial, these divisions greatly facilitated consideration of the material.

The first group was composed of the 4 specimens (8 per cent) which contained unequivocal evidence of well-recognized forms of renal disease. These were membranous glomerulonephritis (3 cases) and pyelonephritis (1 case). Although the occurrence of other forms of renal disease is not excluded by these findings, they do suggest membranous glomerulonephritis as the most frequent disorder.

The relationship between overt lesions such as membranous glomerulonephritis and proteinuria is obvious. Although not widely recognized, it has been known for some time that patients with subsiding acute glomerulonephritis or latent pyelonephritis may sporadically exhibit an orthostatic-type pattern of protein excretion.[8,12,13] In addition, recent clinical reports have indicated that at least 25 per cent of patients with fixed and reproducible orthostatic proteinuria exhibit clinical evidence of parenchymal renal disease at the end of an average 6-year period of follow-up study.[7] Our observations offer histologic confirmation of this clinical impression but suggest a lower incidence. However, a follow-up biopsy survey of our cases at a later date might well reveal a higher incidence of parenchymal disorder. It is of interest to contrast our figure of 8 per cent with the much higher incidence of unequivocal abnormality found in biopsy studies of patients with asymptomatic persistent proteinuria.[14,15]

The second group consisted of 23 cases (45 per cent) in which there were varied alterations of insufficient intensity or specificity to justify a conclusive pathologic diagnosis. Cases with capillary wall thickening accounted for 80 per cent (18 biopsies) of this group. The remainder exhibited 3 or more of the other glomerular changes listed in Table I. The pattern of glomerular alteration observed here was characteristic enough

to permit the designation of a "typical" profile of glomerular involvement. Such a glomerulus exhibited moderate tuft enlargement with focal hypercellularity, cytoplasmic enlargement of epithelial cells, focal or diffuse capillary wall thickening with a normal PAS-positive basement membrane structure, slight capsular thickening, and small clusters of eosinophilic granules within the capsular space. This pattern was largely felt to be the consequence of an altered epithelial component in the capillary wall. However, the observation of a definitely thickened basement membrane in 5 specimens indicated that involvement of this structure may also occur. In the main, studies with electron microscopy supported these opinions and will be reported in another communication.[11]

Forty-seven per cent of the cases were placed in the third group. The majority of these specimens contained none of the specific alterations listed in Table I. Most of the tissue was identical to that obtained from the normal volunteer subjects. However, in a few instances, one or more of the changes described in other cases was noted. These alterations lacked sufficient association with others to warrant their inclusion in the second group. Most cases of this type were characterized by eosinophilic granules within the capsular space beside an otherwise normal glomerulus. Although adequate proof is lacking, these droplets were felt to represent protein-containing material which had traversed the glomerular capillary wall. Their presence in the otherwise normal kidneys of patients with orthostatic proteinuria, but not with certainty in normal volunteers, suggests the existence of an underlying ultra-microscopic defect which is not identifiable by conventional microscopy. If so, the actual incidence of glomerular defects in fixed and reproducible orthostatic proteinuria is much higher than our results have shown. Similarly "normal" kidney tissue has been described in light microscopic investigations of other proteinuric states in which ultra-microscopic defects were subsequently found.[16,17]

The exact cause and clinical significance of these nonspecific glomerular alterations is uncertain. More than one causative factor may well be responsible for their appearance. It is logical to assume that they are causally related to this form of asymptomatic proteinuria. If such is the case, it is possible that they simply represent benign structural defects which are nonprogressive and unrelated to overt renal disease. They also may be viewed, however, as either the healed residua of a previous bout of renal disease or as the first manifestation of an undefined form of future renal disease. Both the results of King's serial clinical studies[7] and the observation of more advanced capillary wall thickening in 5 cases in the present study imply that the latter possibility is a strong one. Careful and well-controlled serial biopsy studies of these patients are

needed if we are to document the eventual histologic evolution of the glomerular changes. Meanwhile, the precise long-term prognosis of patients with fixed and reproducible orthostatic proteinuria must be considered undetermined and with reservation.

In the past, considerable discussion has been directed toward the relative importance of tubular versus glomerular factors in the genesis of various proteinuric states.[8,18–22] The predominance of well-defined glomerular alterations in our patients suggests that fixed and reproducible orthostatic proteinuria is primarily of glomerular origin. Although the possibility of tubular dysfunction cannot be excluded completely, no histologic evidence of tubular difficulty in relation to protein absorption or disposal was observed.

Despite inadequate understanding of the cause of these alterations, their existence does provide a satisfactory explanation for the results of recent renal hemodynamic studies in patients with this type of proteinuria. For many years, orthostatic proteinuria was attributed primarily to postural renal hemodynamic adjustments such as a fall of blood flow or an elevation of renal venous or intra-glomerular pressure.[1,4,23] This concept implied a difference between the hemodynamic response in upright normal nonproteinuric subjects and patients with orthostatic proteinuria. Recent investigations have shown that this is not the case.[24,25] After standing, similar changes of blood flow, glomerular filtration rate, and filtration fraction have been found in both normal individuals and those with orthostatic proteinuria. These observations indicate that factors other than those of a hemodynamic nature must be of primary importance in the genesis of orthostatic proteinuria.

We feel that a fixed anatomic alteration of the glomerular capillary wall is the initial and fundamental cause of this type of proteinuria. It is this capillary defect which permits the renal hemodynamic adaptations which normally occur on standing to effect an increased transfer of protein into the glomerular filtrate. Thus, although still of importance, hemodynamic factors may be relegated to a secondary or "permissive" role, and an abnormal postural hemodynamic response need not be invoked to explain the occurrence of fixed and reproducible orthostatic proteinuria.

Summary

Fifty-eight percutaneous renal biopsy specimens were obtained from 56 patients with fixed and reproducible orthostatic proteinuria. Evidence of a well-defined form of parenchymal renal disease was found in only 8 per cent. Forty-five per cent revealed distinctive glomerular alterations characterized by capillary wall thickening without basement mem-

brane thickening, focal hypercellularity, slight capsular thickening, and the presence of eosinophilic granules within the capsular space. The remaining cases showed either normal tissue or occasional isolated alterations of questionable significance.

It is concluded that an underlying anatomic defect of the glomerulus is the initial cause of most, if not all, instances of fixed and reproducible orthostatic proteinuria. The possible relationship of these alterations to parenchymal renal disease is discussed.

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We gratefully acknowledge the generous aid and support of Lieutenant Colonels Wilbur L. Kenoyer and David Auld, Major Milton J. Smith, and the medical house staff of the USAF Hospital, Lackland. We are especially indebted to Dr. C. T. Ashworth for his helpful advice and criticism.

[*Illustrations follow*]

Legends for Figures

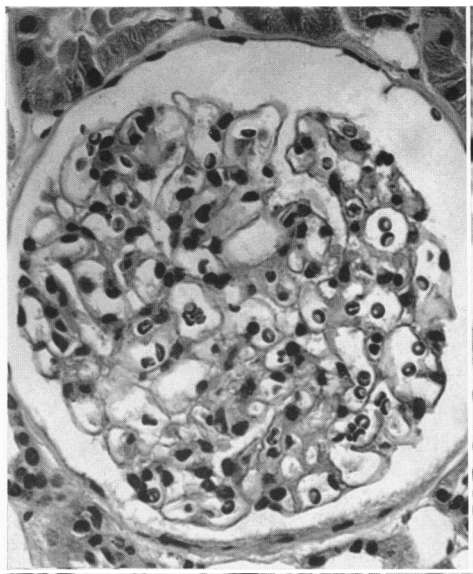
Except where indicated, the photomicrographs were prepared from sections stained with hematoxylin and eosin.

Fig. 1. Normal glomerulus from a young man without evidence of renal disease or proteinuria. All capillary loops are patent and well formed. × 350.

Fig. 2. Portion of a normal glomerulus from a young man without evidence of renal disease or proteinuria. Capsular epithelium is at B. The thin and delicate capillary wall structure is indicated by the arrow. Epithelial cytoplasm is compact. × 700.

Fig. 3. Glomerulus from a young man with fixed and reproducible orthostatic proteinuria. Areas of moderate capillary wall thickening are indicated by arrows. Focal areas of collapsed capillary lumens can be seen. × 300.

Fig. 4. Glomerulus from a patient with orthostatic proteinuria. The majority of the capillary walls are thickened. Several foci of hypercellularity (A) are seen at the periphery of the tuft. Capillary lumens are either small or obliterated within these areas. The walls of capillaries with widely patent lumens appear less thickened. × 400.



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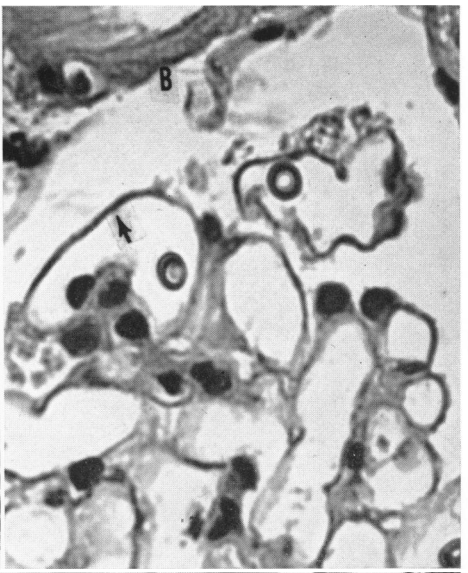

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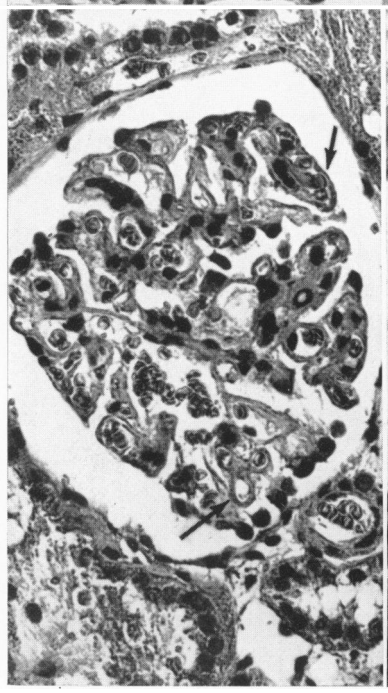

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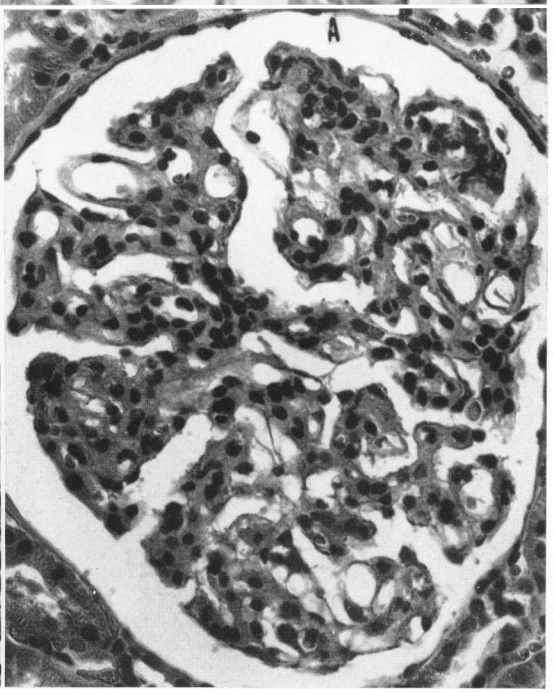

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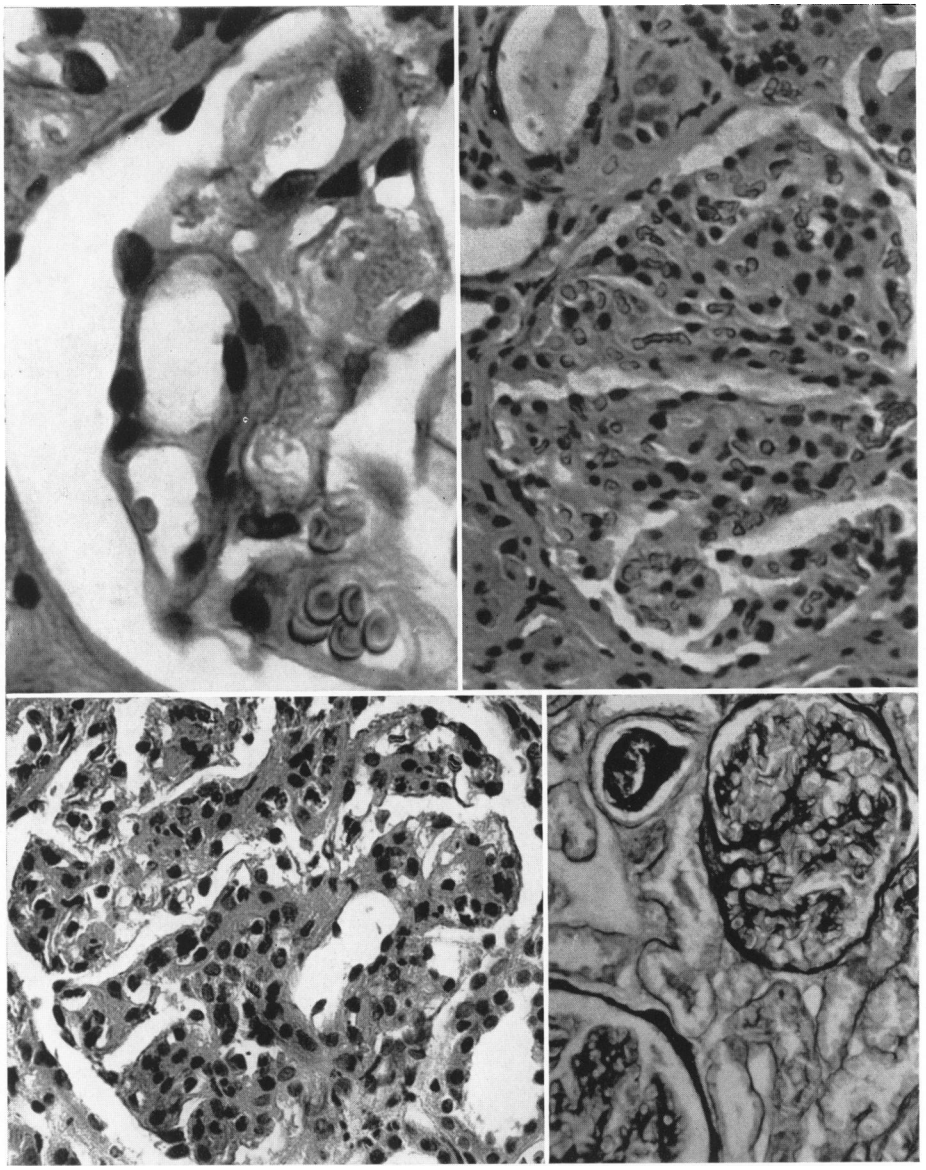

FIG. 5. Focally thickened glomerular capillary walls are widely patent, rigid, and devoid of their normal resiliency. × 750.

FIG. 6. An enlarged glomerular tuft completely fills the capsular space. Capillary lumens have been partially obliterated by thickened capillary walls. A dilated tubule containing an intraluminal cast may be seen at the upper left. × 300.

FIG. 7. The characteristic lesion of membranous glomerulonephritis is illustrated. Pronounced capillary wall thickening, obliteration of the capillary lumens, focal hypercellularity, and early lobulation are evident. The tuft is adherent to the capsular epithelium at one point. × 350.

FIG. 8. Focal condensations of PAS-positive glomerular basement membrane substance and minimal thickening are seen. An intraluminal tubular cast is also apparent. Periodic acid-Schiff stain. × 175.

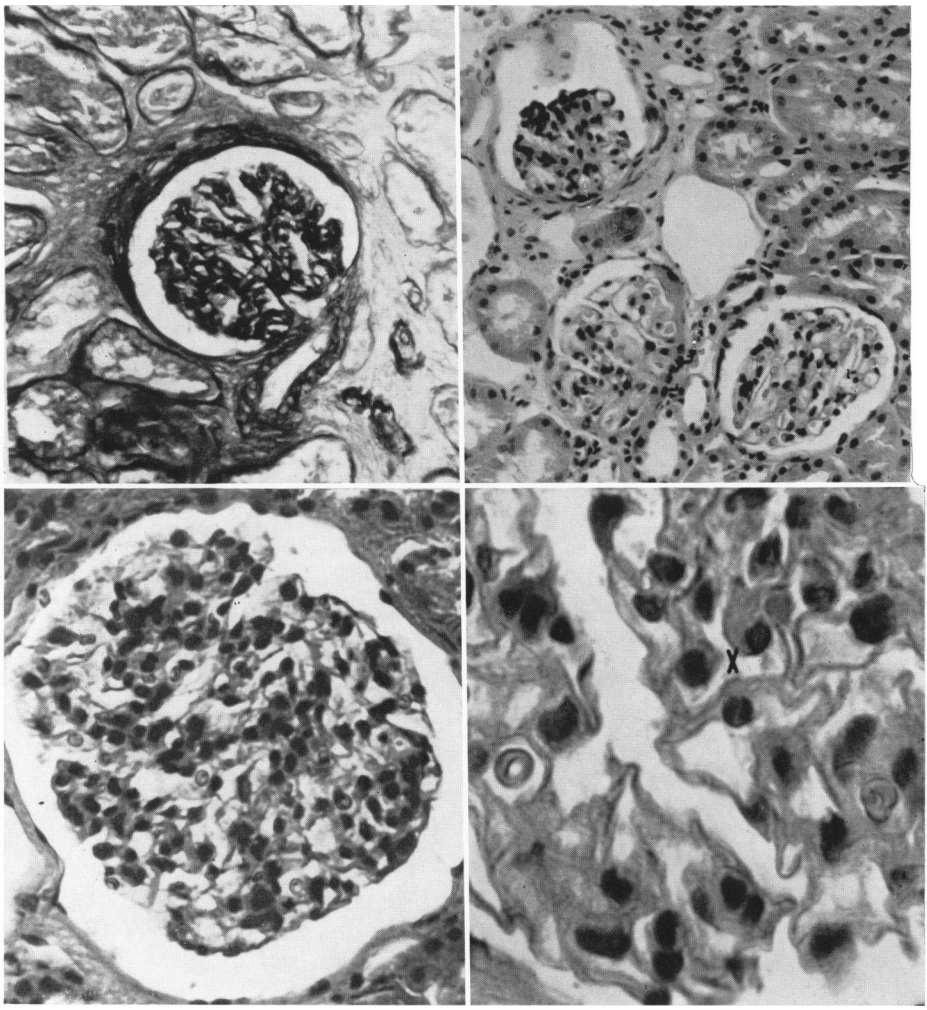

FIG. 9. Advanced basement membrane and capsular thickening in a patient with proteinuria and membranous glomerulonephritis. Pericapsular interstitial fibrosis is seen. Periodic acid-Schiff stain. × 150.

FIG. 10. Three glomeruli from a case of orthostatic proteinuria. Focal hypercellularity and minimal focal capillary wall thickening are noted. × 100.

FIG. 11. Focal hypercellularity and minimal focal capillary wall thickening are manifest. × 300.

FIG. 12. There is minimal capillary wall thickening. The epithelial cells appear enlarged and contain an abundance of cytoplasm (X). × 700.

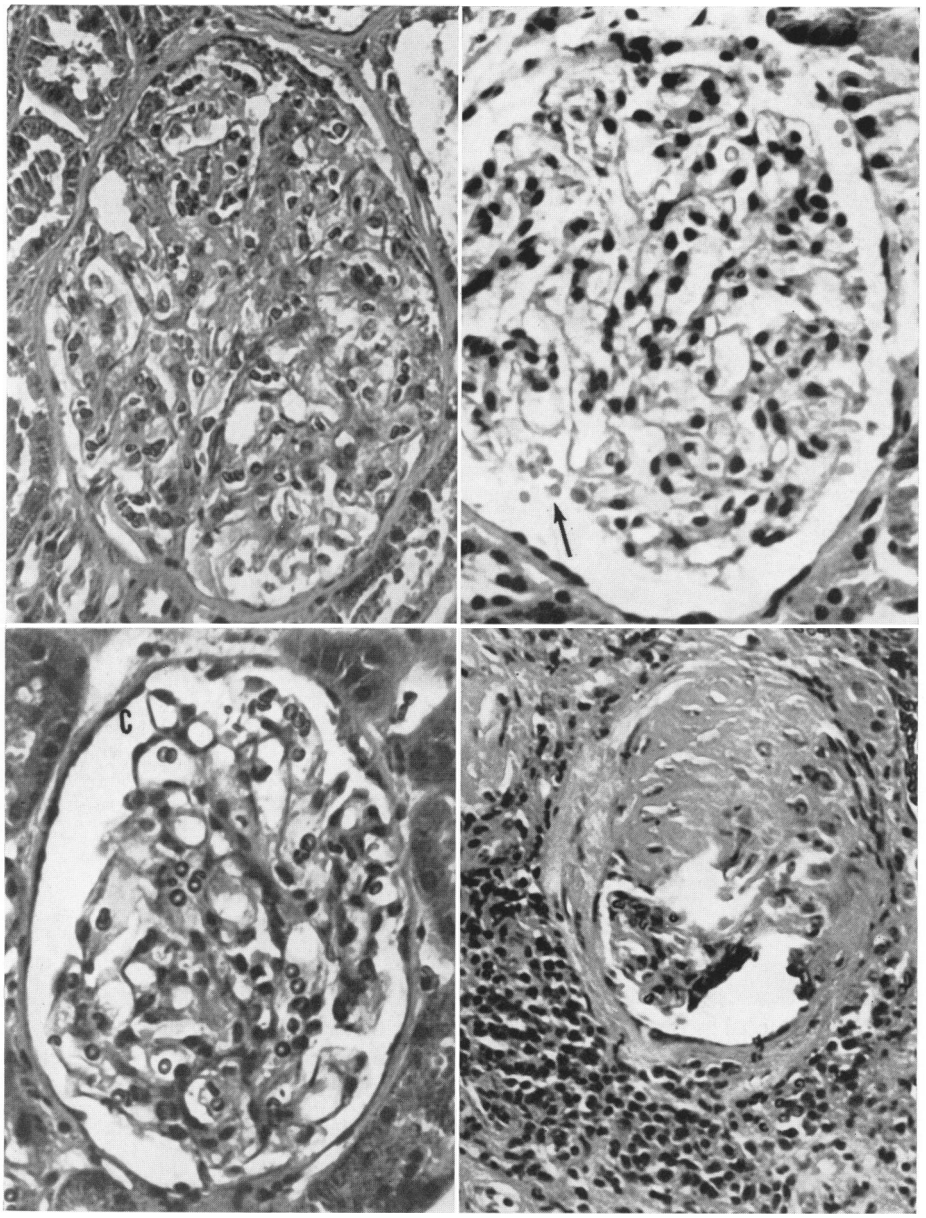

FIG. 13. The tuft is enlarged and there are slight capsular thickening, minimal focal capillary wall thickening, and delicate fibrinous adhesions. × 350.

FIG. 14. Clusters of variably sized eosinophilic granules are noted within the capsular space adjacent to the periphery of the glomerular tuft. The capillary wall structure appears essentially normal in this case. × 350.

FIG. 15. Orthostatic proteinuria. The glomerulus shows minimal capillary wall thickening. At C the walls are stiffened and appear delicately attached to the capsular epithelium. × 325.

FIG. 16. Glomerular fibrosis and active periglomerular inflammation in a case with orthostatic proteinuria. A histologic diagnosis of pyelonephritis was made. × 300.