

Massive Obesity and the Kidney

A Morphologic and Statistical Study

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The renal morphology of 5 grossly obese patients with normal renal function and many of the features of the Pickwickian syndrome was studied at autopsy. The most striking feature was that of increased glomerular size. Measurements of two parameters of glomerular areas indicated statistically significant glomerular enlargement for both as compared to controls. Glomerulomegaly was primarily the result of vascular dilatation and a variable mesangial component. This abnormality was related to several factors, including increased blood volume, hypoxia, and increased right ventricular pressure. Polycythemia, commonly noted in other similar conditions with glomerulomegaly, is believed to be of no importance in the pathogenesis of glomerular enlargement. (*Am J Pathol* 81:117-130, 1975)

MORPHOLOGIC ABNORMALITIES of the kidney in massive obesity have rarely been emphasized in studies of either obesity or the kidney. Glomerular enlargement, as a feature, has been commented upon only once previously.¹ However, renal functional abnormalities, including proteinuria^{2,3} and the nephrotic syndrome,⁴ have been described. To observe and further define renal and glomerular morphology in massive obesity, the kidneys of 5 affected patients were studied at autopsy.

Materials and Methods

Five grossly obese male patients, ranging in age from 3 years, 7 months to 30 years were evaluated. Three were affected with the Prader-Willi syndrome,^{5,6} and 2 with obesity of unknown etiology. The clinical charts were reviewed completely to determine the duration of the obese state; the presence or absence of renal functional abnormalities; a history of renal disease; or clinical evidence of hypertension, cardiac, respiratory or hepatic disease, diabetes mellitus, excess growth hormone secretion, or sickle cell anemia or other hematologic abnormalities. For each patient, a kidney of an age-matched control was studied. These controls were patients who had died of a condition excluding cardiovascular, respiratory, hepatic, renal, hematologic, or metabolic diseases and from whom adequate renal tissue and clinical records were available. Generally, the control patients had died of trauma or central nervous system disorders.

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Gross examination of the kidneys included careful observation of structure and recording of weights. For microscopic study, portions of each kidney were fixed in 10% neutral buffered formalin, dehydrated in the usual manner, embedded in paraffin, sectioned at $3\ \mu$, and treated with hematoxylin and eosin and periodic acid-Schiff stains. Frozen sections of formalin-fixed tissue were stained with oil red O. Glomerular size was measured with an eyepiece micrometer at a magnification of 450 times. All glomeruli (except those obviously distorted by artifact) encountered in the tissue sections were measured until 100 were evaluated—regardless of the plane of section—utilizing the techniques described by Bauer and Rosenberg⁷ and Hutchins and Kutchemeshgi.⁸ The former method consists of measuring the maximum distances across Bowman's capsule in two directions perpendicular to each other, while in the latter method maximum dimensions of the glomerular tuft are measured also in two directions at right angles. The areas of Bowman's capsule and the glomerular tuft were calculated by the formula $\pi ab/4$, where a and b are the two lengths measured. If Bowman's capsule and the glomerular tuft were truly elliptical in shape, the dimensions measured would be the major and minor axes, and the formula would give the exact area. As these structures are almost elliptical, the formula used gives a close approximation to the true area.⁷

The purpose of the statistical evaluation was to determine whether there was a statistically significant difference between the areas of Bowman's capsule or the glomerular tuft in a subject and the age-matched control. A secondary objective was to determine whether the range of areas differed in subject and control. If an ellipsoid is cut at random by a plane (this occurs when the kidney is sectioned as the glomerulus is approximately an ellipsoid), the areas of the resulting ellipses will not form a symmetrical gaussian distribution; there will be a relative excess of smaller areas, causing the distribution to be skewed to the left.⁹ However, the degree of non-normality is not sufficiently great to invalidate the two-tailed Student t test for the difference of the means of two groups of independent observations with unequal variances.¹⁰ This test was accordingly employed. The computations were carried out using a computer program of the Health Sciences Computing Facility at the University of California, Los Angeles. An F test of the variances was also carried out.

Results

The pertinent clinical and laboratory information is presented in Tables 1 and 2. It should be noted that Patients KC, JH, and RM had the constellation of clinical findings and historical milestones that are presently known as the Prader-Willi syndrome. Briefly, this is characterized during antenatal development by decreased intrauterine movements, during early infancy by extreme muscle hypotonia and feeding difficulties, and by a voracious appetite and extreme obesity beginning in early childhood. Developmental milestones are significantly delayed. Characteristically, the hands and feet are small, and the massive fat deposition is generally truncal in location. Males are affected and recognized considerably more frequently than females, mainly because of hypoplasia of the penis and cryptorchidism, which are constant findings. Diabetes mellitus, of the adult onset variety, is present in approximately 30% of the patients and is generally mild. Mental deficiency is a necessary diagnostic feature, and short stature is present in almost all cases. The etiology of this disorder is unknown, although it has been suggested that a congenital lesion of the

Table 1—Clinical Characteristics

Patient	Diagnosis	Age (yrs)	Duration of obesity	Height (cm)	Weight (kg)	Pickwickian syndrome	BP*	CHFT
KC	Prader-Willi syndrome	3.6	19 mons	96.5‡	29§	Yes	125/0	No
JH	Prader-Willi syndrome	14.7	12 yrs	148.5	150	Yes	120/70	No
RM	Prader-Willi syndrome	22	19 yrs	164	202	Yes	110/60	Mild
WP	Massive obesity	26	21 yrs	170	159	Yes	180/110	Mild
MG	Massive obesity	30	27 yrs	163	196	Yes	150/90	No

* Blood pressure prior to terminal events.

† Presence of congestive heart failure.

‡ Tenth percentile.

§ Greater than 97th percentile.

Table 2—Pertinent Laboratory Data

Patient	Hgb/Hct (g%)	p _a O ₂ (mm Hg)	p _a CO ₂ (mm Hg)	Urine		BUN (mg%)	Glucose (mg%)
				Protein	SG		
KC	13.0/39.8	ND	ND	Negative	1.026	13	92
JH	14.2/42.2	70	50	Negative	1.028	13	128
RM	12.8/46.1	48	62	ND	ND	16	102
WP	17.5/52.5	96	34	3+	1.020	11	215
MG	17.7/55	74	57	Negative	1.032	11	105

SG = specific gravity, BUN = blood urea nitrogen, ND = not done.

hypothalamus would explain the varied findings in this entity. To date, however, morphologic abnormalities of any portion of the central nervous system have not been described or noted.¹¹

Patients JH, MG, and WP expired from infectious complications 3, 57, and 259 days, respectively, following jejunioileal bypass surgery. Patient KC, following 13 months of increasing somnolence, died of aspiration pneumonia, and Patient RM died after a single episode of fresh, massive pulmonary emboli. In most instances, the results in Tables 1 and 2 are from determinations made prior to preterminal or terminal events, or prior to the jejunioileal bypass procedures. Therefore, at the time that the data were collected, the patients were in their usual states of health.

It may be seen that all patients had many of the features of the Pickwickian syndrome, i.e., a constellation of signs and symptoms which include marked obesity and somnolence, and alveolar hypoventilation with hypoxia and hypercarbia, right ventricular failure and frequently, but not always, polycythemia.^{12,13} In addition, JH had "borderline" or "chemical" diabetes, manifested occasionally by mild hyperglycemia and requiring no specific therapy. Patient WP was overtly diabetic; this became evident following surgery.

The summary of postmortem findings is indicated in Table 3. All patients had cardiomegaly with both right and left ventricular hypertrophy. The lungs were considerably atelectatic, especially the lower lobes. Aside from fatty metamorphosis, no significant hepatic alterations were evident. The weights of the kidneys were generally increased above the normal adult mean of 313 g. However, renal weight is said to be approximately 0.3% of the body weight in the adult¹⁴; using this criterion, the combined weights in all patients were not greater than that which would be expected. The gross appearance of all kidneys was generally similar and bilaterally symmetrical. Smooth capsular surfaces, widened cortices and absence of scarring were observed for Patients KC, JH, RM, and MG, while the capsular surface of Patient WP demonstrated mild granularity.

Table 3—Summary of Postmortem Findings

Patient	Age (yrs)	Weight (g)	Heart		Lungs			Kidney (combined weights)
			RV (cm)	LV (cm)	Significant atelectasis	Vascular evidence of hypertension	Liver	
KC	3.6	150 69*	0.4	1.0	Yes	No	Fatty meta- morphosis	170 103*
JH	14.7	365 220*	0.4	1.5	Yes	No	Fatty meta- morphosis	270 200*
RM	22	550	0.5	1.8	Yes	No	Fatty meta- morphosis	440
WP	26	385	0.4	1.8	Yes	No	Fatty meta- morphosis	315
MG	30	350	0.4	1.4	Yes	No	Fatty meta- morphosis	450

RV = right ventricular thickness,
LV = left ventricular thickness.
* Expected for age.

Comparison of the measurements is presented in Table 4. With respect to the data on Bowman's capsule, it may be seen, as expected, that glomerular size increases with age in the controls; there is no clear indication of trend of size with age in the obese patients. There is statistically significant enlargement of glomeruli in obese patients as compared to the controls. The differences are, in fact, so great that they do not require statistical methods to demonstrate. Parallel results are obtained for the measurement of the glomerular tuft diameters. The *F* test showed that, in all cases, the variances (the square of the standard deviation) of the areas of Bowman's capsule and the glomerular tuft were greater in the obese subjects than in the respective controls. This result means that the range of areas was greater in the obese than in the normal controls. However, if the standard deviation is divided by the mean, the values obtained for each patient and control are essentially the same. This finding is consistent with the idea that, in the obese patients, increased glomerular size is due to an essentially equal enlargement of all of the glomeruli and not to a gross enlargement of some of them, with the remainder having the same size as in the normal subjects.

The microscopic appearance of both kidneys of all patients was similar (Figures 1-6). Observed was enlargement of glomeruli, contributed to

Table 4—Comparative Measurements of Glomerular Sizes

	Age (yrs)	Mean area (sq μ)	SD	SD/Mean
Bowman's capsule				
Control	3.6	6,654	1,647	0.25
KC		16,264	4,872	0.29
Control	14.8	10,043	2,167	0.21
JH		26,898	6,305	0.23
Control	22	13,653	3,280	0.24
RM		21,910	5,604	0.25
Control	26	15,966	3,204	0.20
WP		22,981	7,241	0.31
Control	30	18,410	5,045	0.27
MG		28,881	9,025	0.31
Glomerular tuft				
Control	3.6	5,187	1,415	0.27
KC		12,460	4,115	0.33
Control	14.8	8,168	1,960	0.23
JH		21,215	5,466	0.25
Control	22	11,190	2,717	0.24
RM		17,715	4,922	0.27
Control	26	13,339	2,842	0.21
WP		18,642	6,955	0.37
Control	30	15,491	4,567	0.29
MG		21,438	8,124	0.37

One hundred measurements were made for each case; in all instances, $P < 0.0001$.

mainly by a mild dilatation of capillaries and an increase in cellularity which was mainly of mesangial origin with a small endothelial component. At times, a modest increase in mesangial matrix in axial regions was present. This change was most prominent in the glomeruli of Patient WP. Capillary basement membranes were thin and delicate. Dilatation of afferent and efferent arterioles was present, although not to a striking degree. Modest hyperplasia of occasional juxtaglomerular apparatuses was evident. Obsolescent glomeruli were rare and comprised considerably less than 1% of the total glomerular population. Neutral fat was not demonstrated in any of the glomeruli.

Significant tubular and interstitial changes were not appreciated. The cells of a few scattered proximal convoluted tubules contained a variable but small number of neutral fat droplets.

Alterations specific for, or compatible with, diabetic nephropathy were absent in all patients.

Discussion

This study indicates that in the absence of renal functional abnormalities, glomerular morphology may be altered in massively obese patients. This alteration is in the form of significant glomerular enlargement, mild hypercellularity, and variable widening of mesangial regions. Capillary and arteriolar dilatation are regular features.

Glomerular enlargement in massive obesity has rarely been observed. Probably the only comment upon this association was by Suzuki,¹ who described a patient with obesity, the Pickwickian syndrome, and endocardial fibroelastosis. No mention is made of the hematocrit or hemoglobin levels, but proteinuria was present. The patient died in cardiac and hepatic failure. The kidneys were grossly enlarged, and the glomeruli were congested, hypercellular, and significantly enlarged when compared to controls. The mesangium was not commented upon, nor the increased cells identified. Suzuki related the glomerulomegaly to prolonged hypoxemia.

A large variety of extrarenal disorders has been associated with glomerulomegaly. Perhaps the best studied of these is the glomerular lesion associated with cyanotic congenital heart disease. It was first described by Meeson and Litton,¹⁵ who noted enlarged glomeruli with dilated capillaries, arterioles and veins. Bauer and Rosenberg,⁷ in one of the first complete and elegant quantitative studies of glomerular enlargement, described glomerulomegaly and noted hypercellularity and increase in mesangial matrix in some cases. Spear¹⁶ emphasized mesangial abnormalities consisting of hypercellularity and, at times, considerable

widening. Also noted in selected cases was hyalinization of both afferent and efferent arterioles, similar to that seen in diabetes mellitus.¹⁷ All of the patients studied by these investigators and by others¹⁸⁻²¹ had severe hypoxia, polycythemia, and increased right ventricular pressure in common, and the renal alterations were attributed either to hypoxia or polycythemia and its hemodynamic effects.

Glomerulomegaly has also been described in various chronic lung diseases,^{22,23} chronic cor pulmonale,²⁴ and right-sided congestive heart failure.⁸ In these disorders, the stimulus for glomerular enlargement was thought also to be either hypoxia, polycythemia, or the hemodynamic effects of increased right ventricular pressure.

In a study of renal abnormalities in children at high altitudes, Naeye²⁵ attributed glomerulomegaly to several factors, including increased blood volume and viscosity, arterial hypoxemia, and reduced renal parenchymal oxygen tension. He also suggested that the glomerular changes may result in an increased glomerular filtration surface. In a study of parabiotic twins, Naeye²⁶ noted that the polycythemic ones had more mature and larger glomeruli; this was also attributed to increased blood volume and hypertension.

Although polycythemia is a feature of many of the conditions noted above and has been implicated as a causal mechanism producing enlarged glomeruli, there have been conflicting reports regarding this association. Corrin,²⁷ in a quantitative study, found no increase in glomerular size in 5 patients with polycythemia vera and 1 with polycythemia associated with cerebellar hemangioblastoma. Similarly, Spear¹⁶ observed no alterations in 9 patients with polycythemia vera. Hamburger *et al.*,²⁸ studying renal biopsies of 4 cases of polycythemia vera, described dilated glomerular capillaries as the sole abnormality. Kindred,²⁹ studying the effects of varying barometric pressures on the kidneys in rats, showed that renal congestion and glomerular enlargement were related to the degree of anoxia and not to the erythrocyte count. Alternatively, Howenstine *et al.*³⁰ noted glomerular enlargement in all 24 patients with proteinuria and polycythemia of diverse cause, including 5 with polycythemia vera. Malizia³¹ noted glomerular enlargement in 14 patients with polycythemia and cyanotic congenital heart disease, 2 with polycythemia vera, and 2 with "chronic cyanotic emphysema" and polycythemia.

The obese patients in this study may help to elucidate the differing results alluded to above. Polycythemia was only of a mild degree in 2 patients and not at all present in 3 others. However, as indicated in studies by Alexander *et al.*³² and Rochester and Enson,³³ among others, massively obese individuals have significantly increased blood volumes. It would ap-

pear that it is not the hematologic abnormality but the blood volume alteration and its resultant hemodynamic effects that are partly responsible for glomerular enlargement. Perhaps, significant blood volume increase combined with either a cardiac and/or respiratory defect causing hypoxia and elevated right ventricular pressure are necessary to produce glomerulomegaly. It may well be that those polycythemic patients without glomerulomegaly in the studies referred to above did not have the added cardiac or pulmonary insult.

The patients described herein have had longstanding massive obesity and many of the features of the Pickwickian syndrome during their main growth period. These features and increased blood volume are also common to almost all of the previously mentioned conditions associated with glomerulomegaly. It is postulated, therefore, that the glomerular enlargement observed in these grossly obese patients is related to a variety of factors. Tissue hypoxia, as a result of hypoventilation and hypoxemia, increased blood volume with its hemodynamic sequelae, and the mechanical effects of right ventricular hypertrophy cause arteriolar and capillary dilatation and may, in some undefined manner, also affect the mesangium. Because immunofluorescent studies were not performed in this study, it is not possible to comment upon the findings of Spear and Kihara,³⁴ who noted staining by antihuman Fraction II antiserum in 2 patients and deposition of γ -globulin in the mesangium of 1 patient with cyanotic congenital heart disease.

The results of the neutral fat studies in these patients contrast sharply with those of Counihan,³⁵ who found in 1 massively obese patient such large aggregates of fat in the tubules that they were visible grossly as golden granules.

As diabetes mellitus may be seen in patients with the Prader-Willi syndrome, and as Patients JH and WP were diabetic, it is of importance to exclude diabetes as a cause of glomerular enlargement. The usual morphologic glomerular diabetic manifestations were completely lacking in all 5 patients. Although enlargement of glomeruli and tubules has been noted in diabetics, it is in those kidneys affected with glomerulosclerosis, rather than in structurally normal ones.³⁶ The mesangial abnormalities of Patient WP, however, cannot definitely be excluded from a diabetic origin.

In the patients described here, constant renal functional abnormalities had not resulted, although, in view of the relatively frequent finding of proteinuria in massive obesity, the morphologic changes may be contributory. The recent report by Weisinger and co-workers⁴ of the nephrotic syndrome complicating massive obesity appears to be unrelated

to this discussion, for the kidney biopsies of their 2 patients so studied indicated the presence of the lesions of focal and segmental glomerulosclerosis and hyalinosis. Glomerular enlargement was not commented upon by these authors.

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[Illustrations follow]

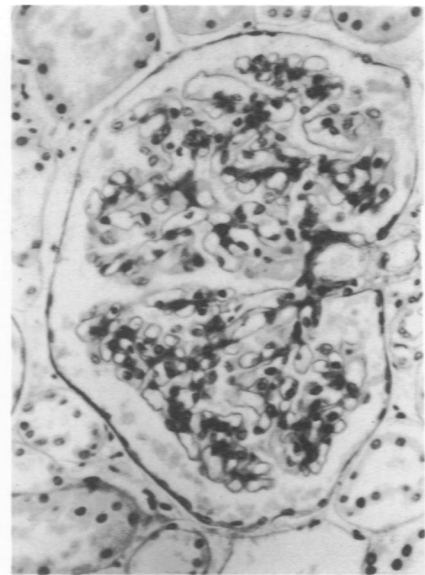
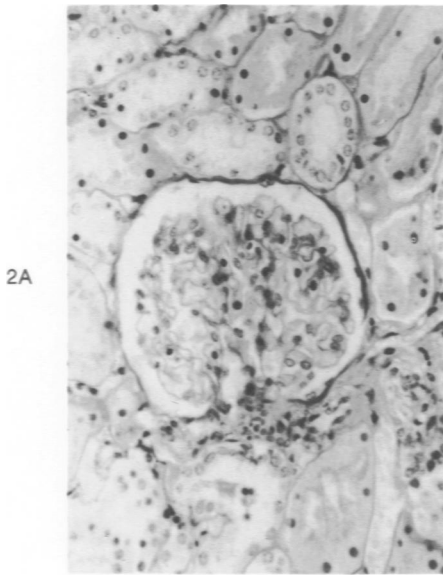
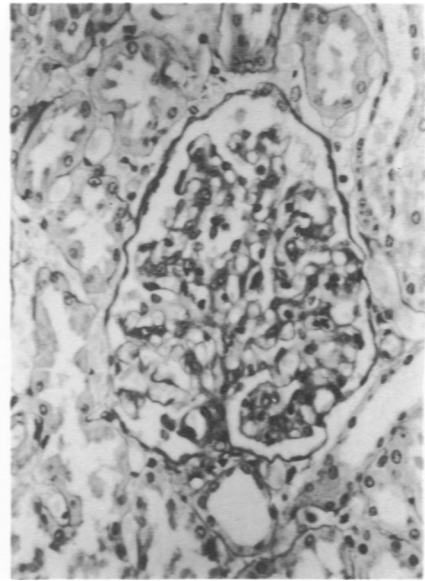
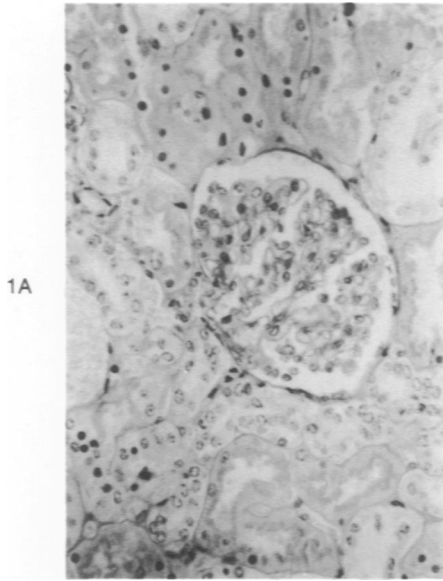
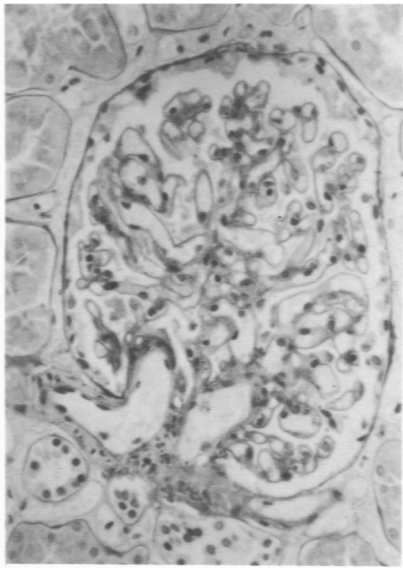
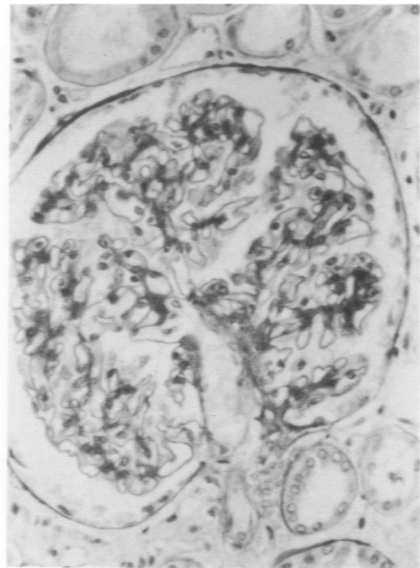


Figure 1—Corresponding sections of glomeruli from control (A) and Patient KC (B) (3.6 years), indicating comparative sizes (periodic acid-Schiff, $\times 250$). **Figure 2**—Corresponding sections of glomeruli from control (A) and Patient JH (B) (14.7 years), indicating comparative sizes (periodic acid-Schiff, $\times 250$).

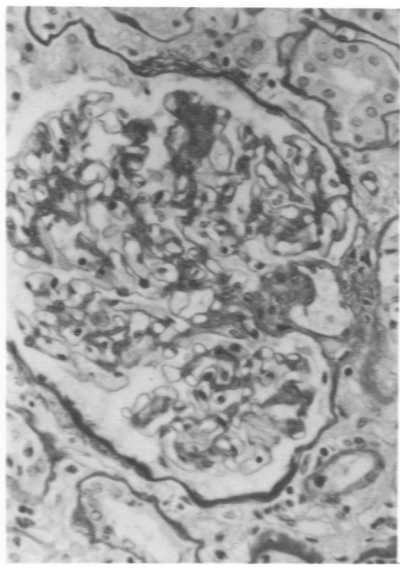
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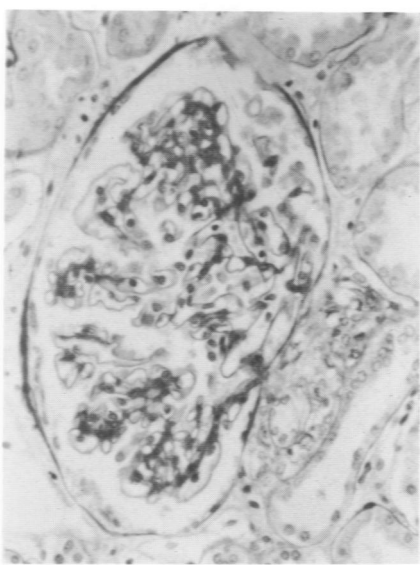
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Figures 3-6—The spectrum of glomerular abnormalities is illustrated. 3—Dilatation of afferent and efferent arterioles is evident at the hilus (periodic acid-Schiff, × 250). 4—Mild increase in endothelial and mesangial cells is present, as are dilated capillaries (periodic acid-Schiff, × 250). 5—Glomerulus with increase in mesangial matrix (periodic acid-Schiff, × 250). 6—Hyperplastic juxtaglomerular apparatus (periodic acid-Schiff, × 250).