POST-STREPTOCOCCAL GLOMERULONEPHRITIS: HISTOPATHOLOGIC AND CLINICAL STUDIES OF THE ACUTE, SUBSIDING ACUTE AND EARLY CHRONIC LATENT PHASES * †

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Most present knowledge of structural changes in the kidneys of patients with clinical acute glomerulonephritis has come from postmortem studies made on the occasional patient who died during the acute phase of the disease. Such studies, particularly those of Langhans (1), Löhlein (2), Volhard and Fahr (3), Bell (4), McGregor (5) and others (6, 7), have given an accurate account of the pathology of severe acute glomerulonephritis and have formed the present source of textbook description.

Mortality during acute glomerulonephritis has been variously estimated as between 2 and 12 per cent (8–13). Another 1 or 2 per cent of patients has died within a year or so after onset, having followed a subacute or persistently active clinical course (2, 3, 9). Most authors have assumed that the renal changes found in the majority of patients who survived the initial acute attack would be qualitatively similar to those noted in the fatal cases, although little direct evidence existed to support this view. Furthermore, it is not known whether any distinctive histologic features characterize the kidneys of those patients who completely recover clinically as opposed to those who develop chronic latent glomerulonephritis.

These problems can now be studied by correlation of the clinical course of glomerulonephritis with structural changes found on percutaneous renal biopsy. A few cases studied by this technique have been published (14–21) and some of our own results have been reported previously in preliminary form (22–24).

The present paper is a report of clinical and histological observations in 36 patients with sporadic clinical acute glomerulonephritis proved in each instance to have followed a Group A hemolytic streptococcal infection. One purpose is to describe in detail the types of lesions found in the kidneys during the acute phase of this disease and to illustrate how they change with time. A second and perhaps more important purpose is to present preliminary data on the types of lesions most commonly associated with the development of early clinical chronic glomerulonephritis. The results suggest that acute post-streptococcal glomerulonephritis is a readily definable disease with fairly characteristic histologic abnormalities. Post-streptococcal clinical glomerulonephritis, both during the acute and early chronic phases, usually can be distinguished from glomerular diseases of non-streptococcal etiology.

MATERIALS AND METHODS

The criteria for selection of patients for a study of the natural history and pathology of acute glomerulonephritis must be rather rigid, since a variety of different primary and secondary glomerular diseases may masquerade under this clinical diagnosis (22, 23, 25).

Patients. The present report is based on observations on 36 patients who presented clinical and laboratory evidence of acute glomerulonephritis or both. The disease followed an infection in 32 patients which was proved to be of hemolytic streptococcal etiology by isolation of Group A hemolytic streptococci on culture and/or by a significant increase in serum antistreptolysin O (ASO), antistreptokinase (ASK) or antihyaluronidase (AH) titers on serial measurement (Table I). History of infection was not obtained in 4 patients but serial changes in ASO, ASK or AH titers indicated a preceding strep-

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TABLE I

Summary of certain clinical data in patients with acute glomerulonephritis *

Patient	Age	Sex	Prior known normal urine	Associated infection	Throat culture	Serum ASO (units) Max.	Serum ASO (units) Min.	Serum T-12 antibodies	Latent period (days)	Comments
						Healed				
Swi	22	♂	11 D	Tonsillitis	BHS	500	100	pos.	25	Hyperthyroidism. Urine normal 14 D after infection
Dil	18	♂	1 M	Cellulitis	ND	2,000	625	neg.	3	Transient erythema multiforme
Ros	20	♂	±1 Y	Pharyngitis	neg.	500	125	neg.	7	Only test for T-12 antibodies at 6 W
Sch	18	♂	3 W	Pneumonitis	BHS	333	125	neg.	±14	Right lower lobe pneumonitis at onset
Shi	20	♂	1 M	Pharyngitis	BHS	166	(4 M)	neg.	±12	Petechiae at onset
Gav	20	♂	±1 Y	Tonsillitis	ND	250	100	pos.	21	First ASO titer at 3 M
Swe	18	♂	±6 M	Pharyngitis	ND	166	50	neg.	6	
Eas	22	♂	3 M	Pharyngitis	ND	333	100	neg.	3	Pneumonitis on roentgenogram at onset
Ser	40	♂	2 Y	Pharyngitis	neg.	500	166	neg.	12	
Mol	18	♂	12 D	Tonsillitis	ND	625	50	neg.	20	Urine normal 8 D after infection
Dix	22	♂	1 M	Uncertain	BHS	333	ND	ND		Pilonidal cyst drained 1 M before; no resp. infect.
Mul	43	♀	None	Pharyngitis	NHS	100	50	pos.	±23	Six others of family developed pharyngitis (B hemol. strep.); these could not be typed but patient and 2 others developed serum antibodies against T-12; 3 of patient's children also developed mild acute glomerulonephritis
Moe	18	♂	±1 Y	Pharyngitis	neg.	333	125	neg.	10	Right lower lobe pneumonia with effusion at onset
Vin	32	♂	4 Y	Tonsillitis	T-12	2,560	625	neg.	17	
Har	30	♀	None	Pharynigtis	ND	333	125	pos.	18	
Roo	66	♂	3 Y	None noted	ND	333	50	neg.		Renal calculus, bladder tumor (successfully removed), mild diabetes
Col	39	♂	None	Pharyngitis	ND	250	83	pos.	14	Chronic dermatitis, type unknown
Eva	18	♂	4 D	Pharyngitis	ND	1,000	200	pos.	11	Three Y, and again 5 D before onset had acute rheumatic fever, no cardiac involvement

* Abbreviations: ASO = antistreptolysin titer. ASK = antistreptokinase titer. AH = antihyaluronidase titer. T-12 = Type 12 hemolytic streptococcus. BHS = beta hemolytic streptococcus. ND = Not done. gr.AHS = Group A hemolytic streptococcus. D = days; W = weeks; M = months; Y = years.

TABLE I—(*Continued*)

Patient	Age	Sex	Prior known normal urine	Associated infection	Throat culture	Serum ASO (units) Max.	Serum ASO (units) Min.	Serum T-12 antibodies	Latent period (days)	Comments
						Healed				
Eik	48	♂	None	Pharyngitis	neg.	333	125	pos.	21	Also had cellulitis; chronic alcoholism
San	24	♂	None	Pharyngitis	neg.	500	50	neg.	40	*S. mansoni* infestation, duodenal ulcer
McC	59	♂	None	Pharyngitis	neg.	500	125	neg.	±10	Arteriosclerotic heart disease
Lee	44	♂	None	"Flu"	neg.	250	100	neg.	±38	Chronic active pulmonary tuberculosis; atypical photochromogenic organism
Mar	57	♂	2 Y	None noted	neg.	625	250	neg.		
						Not healed at last follow-up				
Dra	20	♂	±2 Y	Pharyngitis	ND	250	50	pos.	28	
Byr	17	♂	±6 M	Pharyngitis	ND	500	50	pos.	6	Urticaria after benzathine penicillin G given for pharyngitis
Lar	27	♂	±2 Y	Pharyngitis	ND	125	50	neg.	21	
Rob	20	♂	±2 Y	None noted	ND	166	125	pos.		AH titers 640, 320; ASK titers 1448, 512
Bis	21	♂	±1 Y	Pharyngitis	BHS	125	100	neg.	33	First ASO at 4 M; AH titer 512
Jam	26	♂	7 M	Tonsillitis	T-12	200	83	pos.	14	
Win	20	♂	±1 Y	Pharyngitis	neg.	333	250	ND	15	Only patient in series with positive urine cultures; *E. coli* once *A. aerogenes* twice
Gar	10	♀	None	Pharyngitis	gr. AHS	333	62	neg.	14	
Lat	19	♂	3 W	Pharyngitis	ND	333	50	neg.	42	Transient purpura and arthralgia at onset
Ape	37	♀	1 Y	Pharyngitis	gr. AHS	833	200	neg.	10	
Vla	37	♂	6 M	Pharyngitis	ND	333	100	neg.	28	Pneumonia 21 M after onset; appendectomy 30 M after onset
Tra	19	♂	3 M	Pharyngitis	ND	500	125	neg.	±28	
						Died				
Cal	34	♂	None	Pharyngitis	neg.	400	333	ND	4	Died 32 D after onset

TABLE II

Data concerned with renal disease in patients with acute glomerulonephritis *

Patient	Presenting renal symptoms	Edema	Maximum blood pressure	Urine: Onset Prot.	Onset RBC	Duration Prot.	Duration RBC	Final Prot.	Final RBC	Maximum BUN	Minimum PSP	Duration follow-up	Comments
			mm Hg				*Healed*			*mg %*	*%*	*months*	
Swi	(Urinalysis)	0	140/60	1+	mod.	9.5 M	9.5 M	0	0	12	35	17	
Dil	(Urinalysis)	0	124/84	2+	mod.	7 W	4 M	0	occ.	14		4	
Ros	Gross hematuria	0	120/70	0	gross		1 M	0	0	15	20	5	All urines protein free
Sch	(Urinalysis)	0	158/100	3+	occ.	5 M	4 M	0	0	15	30	7.5	
Shi	Gross hematuria	0	130/80	1+	gross	3.5 M	3.5 M	0	0	17	58	5	
Gav	Gross hematuria	1+	140/80	3+	gross	2.5 M	1 M	0	0	18	35	4	
Swe	Gross hematuria	0	120/90	2+	gross	2.5 M	2.5 M	0	0	20	30	4	
Eas	Gross hematuria	0	146/100	4+	gross	3 M	3 M	0	0	20	25	19	
Ser	Gross hematuria	3+	172/116	4+	gross	3 M	3.5 M	0	0	22	24	26	Transient hematuria at 24 M during Salmonella dysentery
Mol	(Urinalysis)	0	138/60	4+	many	2.5 M	3.5 M	0	0	24	35	8	
Dix	Gross hematuria	0	160/95	3+	gross	2.5 W	2.5 M	0	0	24	25	3	
Mul	Gross hematuria	2+	160/100	3+	gross	4 M	7 M	0	occ.	24		8.5	
Moe	(Urinalysis)	0	180/120	3+	many	8–24 M	7 M	0	0	25		25	
Vin	Gross hematuria	2+	204/116	4+	gross	1 M	1 M	0	0	25	20	4	
Har	Edema	3+	170/108	4+	many	2 M	2 M	0	0	25		6	Steroid therapy begun 2nd month; urea clearance increased from 10 to 46% of normal in 2 W
Roo	Edema	3+	160/90	3+	many	11 M	6 M	0	0	27	2	36	PSP 12%, urea clearance 61% of normal at 5 M
Col	Gross hematuria	3+	166/118	2+	gross	26 M	4 M	0	0	28	21	51	Steroid therapy for 2 M, beginning 5 M after onset; urea clearance increased abruptly from 47 to 80% of normal during therapy
Eva	(Urinalysis)	0	130/90	2+	many	1 M	6.5 M	0	many	33		6.5	
Eik	Edema	4+	200/110	4+	many	1.5 M	1.5 M	0	0	35	20	5	Urea clearance normal at 1 M
San	Gross hematuria	1+	180/110	4+	gross	4 M	16 M	0	0	42	14	26	PSP 36% at 15 M; urea clearance 103% of normal at 19 M

* Abbreviations: Prot. = protein. RBC = red blood cells. Y = year, M = months, W = weeks, D = days. BUN = blood urea nitrogen. PSP = phenolsulfonphthalein excretion, per cent in 15 minutes.

TABLE II—(*Continued*)

Patient	Presenting renal symptoms	Edema	Maximum blood pressure	Urine: Onset Prot.	Urine: Onset RBC	Urine: Duration Prot.	Urine: Duration RBC	Urine: Final Prot.	Urine: Final RBC	Maximum BUN	Minimum PSP	Duration follow-up	Comments
			mm Hg							*mg %*	*%*	*months*	
						Healed							
McC	Edema	2+	200/110	3+	many	3 W	4 W	0	0	45		36	Urea clearance 73% of normal at 4 M
Lee	Edema	3+	126/86	3+	gross	3.5 M	5 M	0	0	66		7	
Mar	Edema, oliguria	2+	175/95	2+	many	4 M	4 M	0	0	128		6	Steroid therapy begun 1 M after onset, for 1 M; urea clearance had been minimal, increased to 29% of normal at end of treatment
						Not healed at last follow-up							
Dra	Gross hematuria	2+	135/85	4+	gross	10+ M	10+ M	4+	many	15	16	10	Developed nephrotic syndrome at 7 M
Byr	Costovertebral tenderness	0	124/80	1+	mod.	4.5+ M	4.5+ M	4+	0	17	15	4.5	Proteinuria increased during observ. period despite bed rest; PSP 30% at 3 M
Lar	Gross hematuria	1+	220/120	4+	gross	37+ M	37+ M	1+	occ.	22	15	37	At 17 M 3 of 13 urines had protein
Rob	Gross hematuria	3+	164/120	4+	gross	4+ M	4+ M	1+	many	24		4	Killed in accident 1 Y after onset; no autopsy
Bis	Gross hematuria	2+	168/110	4+	gross	7+ M	7+ M	1+	occ.	24		7	
Jam	(Urinalysis)	0	134/90	3+	many	40+ M	40+ M	2+	occ.	25	6	40	Hypertension (132/90 to 190/118) during follow-up
Win	Edema	4+	180/110	2+	many	4+ M	4+ M	1+	occ.	39		4	BUN still increased at last observation
Gar	Edema	1+	200/120	4+	few	16+ M	16+ M	1+	few	40		16	
Lat	Edema	2+	138/98	4+	many	45+ M	45+ M	1+	rare	45		45	
Ape	Edema	4+	180/130	4+	many	25+ M	25+ M	2+	many	79	1	25	
Vla	Edema	3+	170/100	4+	many	31+ M	31+ M	1+	few	96	0	31	Steroid therapy 2nd M; marked improvement in urinary findings and anemia during therapy; urea clearance increased from 19 to 73% of normal
Tra	Gross hematuria	0	160/98	4+	gross	8+ M	8+ M	1+	few	200		8	Pericardial friction rub; plasma potassium = 7.0 mEq/L; steroid therapy 1st M associated with dramatic improvement in clinical symptoms, biochemical abnormalities and urine
						Died							
Cal	Gross hematuria	4+	180/116	4+	gross	5 W	5 W	4+	many	179		1	Died 32 D after onset

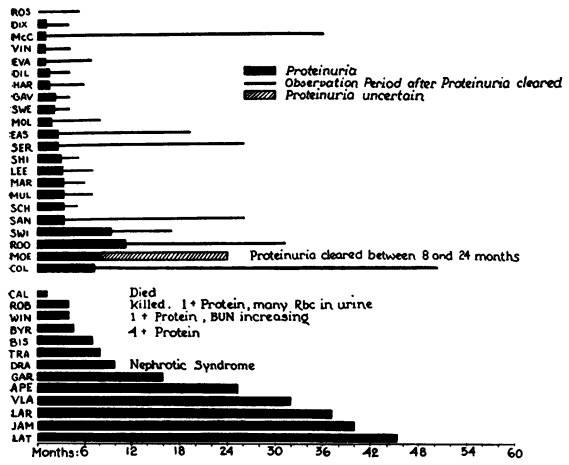


CHART 1. DURATION OF PROTEINURIA AND OBSERVATION PERIOD IN PATIENTS WITH ACUTE GLOMERULONEPHRITIS. There are two errors in this chart: Patient Eik was accidentally omitted from the first group and Col's proteinuria persisted for 26 months, not 8 months as indicated on the chart.

tococcal infection in each of these 4 patients. Evidence that the streptococcus was Type 12 was obtained in 11 of the 33 patients in whom sera were obtained for Type 12 antibodies.

Only patients from whom at least one adequate renal biopsy was obtained within 6 months of the onset of nephritis are included in the present analysis. Pertinent data concerning the patients, their disease and the evidence for preceding streptococcal infection are summarized in Tables I and II. Nineteen of the 36 patients were studied at the United States Naval Hospital, Great Lakes, Ill. The majority of these were transferred to this hospital from elsewhere in the United States or, in several instances, from overseas bases. The remaining patients were studied in hospitals affiliated with Northwestern University Medical School. Evidence of previous diffuse renal disease was not obtained in any of the patients. Records of previously normal urine examinations were available in many (Table I, column 4). Further, the latent period between precipitating infection and the onset of symptoms or signs of acute nephritis exceeded 5 days in 29 of the 33 patients in whom the latent period could be estimated. Latent periods of 5 to 28 days are characteristic of the initial attack of acute poststreptoccocal glomerulonephritis, in contrast to 1 to 5 days of the exacerbation in chronic glomerulonephritis (26).

All but 4 of the patients were males, and all but 7 were less than 40 years of age; 22 were males between the ages of 17 and 25 years; 1 was a 10 year old female. We wish to emphasize that the majority of patients discussed in this report represent instances of sporadic acute glomerulonephritis in the adult. None of the patients contracted the disease under the epidemic conditions so ably described by Rammelkamp (27) and Stetson and colleagues (28) although 1 patient was the second of 4 members of a family of 7 who developed acute nephritis associated with Type 12 streptococcal infections.

Excluded from the present analysis were patients with clinical acute glomerulonephritis in whom we failed to obtain evidence of hemolytic streptococcal infection. This excluded group comprised 10 patients with nonstreptococcal acute nephritis previously reported (22) and 3 additional patients observed since that report. Also excluded were 4 patients who were seen too late to determine with certainty whether or not the associated infection had been of streptococcal origin or in whom the first adequate renal biopsy was obtained more than 6 months after onset. Three patients with poststreptococcal exacerbations in chronic glomerulonephritis likewise were excluded from the present considerations, as was a considerable number of patients studied only during the chronic phase of glomerulonephritis.

Clinical observations. All patients were followed by routine clinical and laboratory techniques. Positive and negative physical findings were recorded. Serial urinalyses and serial measurements of blood urea nitrogen were performed in all patients. Other nitrogenous wastes and electrolytes were determined when indicated. Most had one or more urea clearance determinations. Almost all had urine concentration tests and phenolsulphonphthalein (PSP) excretion tests.

The majority had moderately severe clinical acute glomerulonephritis (see Table II), although the diagnosis in 6 patients who had no renal symptoms was established only by routine examination of the urine following admission to the hospital for infection. Many presented gross hematuria, others malaise, headaches, edema or dyspnea. All but 1 of the patients had proteinuria and all had hematuria, which was gross in 18 of the 36; another 13 patients had many red blood cells in the urinary sediment. The duration of proteinuria and observation periods is shown in Chart 1.

Bacteriologic and immunologic studies. Throat cultures obtained more than 4 weeks after onset of infection are listed in Table I as "not done," as were cultures obtained only after the beginning of antibiotic therapy. Titers of serum antibodies against hemolytic streptococci were measured in all patients. Antistreptolysin O titers were measured by the method of Rantz and Randall (29), antistreptokinase by the method of Christensen (30) and antihyaluronidase by the method of Harris and Harris (31). Variations in antibody titers less than two tubes were not considered significant. Antibodies specific against Type 12 hemolytic streptococci were measured by Stollerman, Kantor and Gordon's modification (32) of the bactericidal method of Todd (33). The blood remaining in the biopsy needle was cultured in each instance in thioglycollate medium. All such cultures were sterile.

Clinical criteria for healing and chronicity. Permanent disappearance of proteinuria (at least 4 protein-free urines obtained over several weeks) was taken as evidence of clinical healing. Many more urines over considerably longer periods of time were obtained in the

TABLE III

Data relating to renal biopsies *

Patient	Approximate time of biopsy: After onset	Disappearance, proteinuria: Before	Disappearance, proteinuria: After	Findings at time of biopsy: Urine: Prot.	Urine: RBC	BUN	Blood pressure	Biopsy: Length	Biopsy: Glomeruli
	days	*days*				*mg %*	*mm Hg*	*mm*	*no.*
				Healed					
Swi	32	256		trace	occ.	12	140/60	8	8
	79	209		trace	occ.		120/60	6	5
Dil	82		27	0	occ.	14	120/80	7	22
Ros	17	no proteinuria		0	rare	15	120/70	3.5	14
Sch	132	7		trace	few	15	122/66	8	36
Shi	120		2	0	0	12	120/70	7	17
Gav	68		23	0	0	18	140/80	2	13
Swe	72	4		trace	few	15	120/85	6	17
Eas	66	24		1+	few	20	128/84	8	11
	115		25	0	0	20	125/80	9	34
Ser	30	60		2+	many	17	136/80	5	6
	80	10		trace	occ.	20	124/80	10	15
	156		66	0	0	14	138/80	5	5
	775		685	0	0	16	126/88	5	5
Mol	22	58		2+	many	19	135/62	3	10
	114		34	1+†	many	15	120/60	8.5	34
	205		126	0	0	8	125/60	6.5	9
Dix	32		3	0	0	17	128/86	8	25
Mul	11	49		trace	occ.	18	140/80	3	10
Moe	170			trace	occ.	18	125/80	9	19
Vin	15	10		1+	few	25	140/96	8.5	5
Har	39	21		trace	many	25	148/96	19	15
Roo	47	306		1+	rare	20	120/70	5	10
	602		249	0	0	22	130/80	5.5	11
Col	66	732		2+	occ.	14	142/100	8	12
	197	603		trace	0	15	128/78	6	12
	1,356		556	0	0	15	115/82	7	9
Eva	144		61	0	many	15	130/80	2.5	13
Eik	24	28		1+	occ.	19	126/90	15	10
San	33	89		1+	occ.	34	156/90	10	7
	73	63		trace	occ.	12	110/52	4	14
	149		61	0	0	19	110/52	4	1
McC	20	2		trace	rare	17	180/90	5	15
Lee	31	74		2+	many	51	126/86	10	16
	158		14	0	0	17	120/80	5	9
Mar	27	39		2+	many	28	148/80	3	5
				Not healed at last follow-up					
Dra	122			4+	many	15	130/84	5	19
Byr	14			2+	many	17	124/80	6.5	20
	115			2+	many	14	120/80	6	21
Lar	79			0‡	occ.	11	145/90	4	35
Rob	97			1+	many	24	120/80	6	6
Bis	146			2+	many	20	110/80	4	7
Jam	28			trace	few	19	134/90	8	9
	1,013			2+	0	14	159/90	10	37
	1,234			2+	occ.	16	140/90	7	12
Win	61			1+	occ.	15	112/70	12	13
Gar	129			3+	few	25	200/120	7	13
Lat	122			1+	few	25	135/95	11	25
Ape	22			3+	many	52	180/100	8	15
	69			2+	occ.	38	140/100	7	14
	307			1+	occ.	18	178/92	7	1
Vla	82			1+	many	45	138/100	6	10
	162			1+	occ.	27	120/72	2	5
Tra	71			1+	occ.	13	135/80	7	15
	186			1+	few	15	130/80	8	11
				Died					
Cal	30			4+	many	179	178/116	10	16

* Abbreviations as in previous tables.
† Urine day before biopsy contained 1+ protein. Many urines before and after biopsy contained no protein.
‡ Previous and subsequent urines contained protein.

TABLE IV

Histologic findings in 36 patients with proved post-streptococcal acute glomerulonephritis

Patient	Case history no.	Biopsy, after onset	Glomeruli	Glomerular changes: Hyalinized glomeruli	Diseased glomeruli	Hypercellularity*	Endothelial prolif.†	Leukocytes per glom.‡	Lobular necroses or scars§	Crescents‖	Adhesions to: Crescents	Adhesions to: Other	Interstitial fibrosis¶: Recent	Interstitial fibrosis¶: Healed	Disease of vessels: Arteries	Disease of vessels: Arterioles	Tubules: RBC or heme casts
		days	*no.*	*no.*				*Healed*	*no.*	*no.*	*no.*						
Swi	9	32	8	0	0	0	0	0/0–1	0	0	0	0	0	0	0	0	0
		79	5	0	0	0	0	0/0–1	0	0	0	0	0	2+	0	0	0
Dil		82	22	0	all	1+	1+, L.S.	0/1	0	1	0	0	0	1+	0	0	0
Ros		17	14	0	0	0	0	0/0	0	0	0	0	0	0	0	0	0
Sch		132	36	0	all	2+	2+, L.S.	0/0–1	0	0	0	0	0	0	0	0	0
Shi	10	120	17	1	a few	±	±, L.S.	0/0	1S	0	0	1	0	1+	0	0	0
Gav		68	13	0	all	2+	2+, L.S.	0/0–1	0	0	0	0	0	1+	0	0	0
Swe		72	17	0	all	1+	1+, L.S.	0/0–1	0	0	0	0	0	0	0	0	0
Eas		66	11	0	all	2+	2+, L.S.	0/0–1	0	0	0	0	0	1+	0	0	few
		115	34	0	all	2+	2+, L.S.	0/0–1	0	0	0	0	0	1+	0	1+	0
Ser	3	30	6	0	all	3+	2+, Dif.	2/13	0	0	0	0	0	0	0	0	0
		80	15	0	all	2+	2+, L.S.	0/1–6	0	0	0	0	1+	0	0	0	0
		156	5	0	all	2+	2+, L.S.	0/2	0	0	0	0	0	1+	0	0	few
		775	5	0	0	±	±	0/0–1	0	0	0	0	0	0	0	0	0
Mol	2	22	10	0	all	3+	2+, Dif.	10/12	0	0	0	0	1+	0	0	0	many
		114	34	0	all	2+	2+, L.S.	0/1–2	3S	0	0	3	0	2+	0	0	few
		205	9	1	all	1+	1+, L.S.	0/1–2	0	0	0	0	0	2+	0	0	0
Dix		32	25	0	all	2+	1+, L.S.	0/4	0	0	0	1	0	0	0	0	0
Mul		11	10	0	all	2+	1+, L.S.	1–3/7–24	0	0	0	0	2+	0	0	1+	few
Moe		170	19	0	all	2+	2+, L.S.	0/0–1	0	0	0	1	0	2+	0	0	0
Vin		15	5	0	all	3+	2+, Dif.	0/5–22	0	0	0	0	1+	0	0	1+	rare
Har		39	15	1	all	2+	2+, L.S.	0/1–6	0	0	0	0	2+	0	1+	1+	many
Roo		47	10	0	all	1+	1+, L.S.	0/1–2	0	0	0	0	0	1+	0	2+	few
		602	11	3	0	0	0	0/0–1	0	0	0	0	0	2+	0	2+	few

* Hypercellularity = total increase in number of cells within glomerulus including both endothelial cells and leukocytes. Almost total obliteration of capillary loops by cells equals 4+ hypercellularity.

† L.S. = lobular stalks; Dif. = diffuse.

‡ Leukocytes per glomerulus = eosinophiles/polymorphonuclear neutrophiles.

§ N = lobular necrosis; S = lobular scar.

‖ hd = healed; hg = healing.

¶ Healed: 0 = no fibrosis; 1+ = occasional tiny periglomerular foci; 2+ = larger cortical scars; 3+ = 50% or more scarring in cortex; 4+ = diffuse fibrosis. Recent: edema with some inflammatory cells and fibrosis on same scale as above.

TABLE IV—(*Continued*)

Patient	Case history no.	Biopsy, after onset	Glomeruli	Glomerular changes: Hyalinized glomeruli	Diseased glomeruli	Hypercellularity*	Endothelial prolif.†	Leukocytes per glom.‡	Lobular necroses or scars§	Crescents‖	Adhesions to: Crescents	Adhesions to: Other	Interstitial fibrosis¶: Recent	Interstitial fibrosis¶: Healed	Disease of vessels: Arteries	Disease of vessels: Arterioles	Tubules: RBC or heme casts
		days	*no.*	*no.*					*no.*	*no.*	*no.*						
								Healed									
Col	8	66	12	1	all	2+	2+, L.S.	0/2–3	2S	4	3	1	2+	2+	1+	0	many
		197	12	1	all	2+	2+, L.S.	0/1–2	3S	1 hd 3 hg	3	4	0	3+	1+	0	few
		1,356	9	3	all	1+	1+, L.S.	0/1–2	0	0	0	2	0	1+	0	2+	0
Eva	1	144	13	0	all	2+	2+, L.S.	0/0–1	0	0	0	0	1+	0	0	0	0
Eik		24	10	0	all	2+	1+, L.S.	1/5	0	0	0	0	0	0	1+	2+	few
San	4	33	7	0	all	4+	3+, Dif.	3/9	0	0	0	0	0	0	0	0	0
		73	14	0	all	2+	2+, L.S.	0/2–3	0	0	0	0	0	0	0	0	0
		149	1	0	all	2+	2+, L.S.	0/0–1	0	0	0	0	0	0	0	0	0
McC		20	15	11	all	2+	1+, Dif.	0/11	0	1	0	0	0	3+	4+	3+	0
Lee		31	16	0	all	3+	1+, L.S.	0/3–9	0	5	5	0	2+	2+	0	2+	many
		158	9	0	all	1+	1+, L.S.	0/0–1	2S	0	0	2	0	2+	1+	1+	rare
Mar		27	5	0	all	3+	2+, Dif.	1/14–30	0	0	0	0	2+	0	0	1+	0
								Not healed at last follow-up									
Dra		122	19	0	all	1+	1+, L.S.	0/0–1	5S	6 hg	6	2	0	3+	0	0	many
Byr		14	20	0	all	2–4+	2–4+, Dif.	1/2	0	3	2	0	1+	0	0	0	few
		115	21	0	all	1+	1+, L.S.	0/0–1	0	0	0	0	1+	0	0	0	0
Lar		79	35	0	all	3+	3+, L.S.	0/0–1	0	0	0	0	0	0	0	0	0
Rob		97	6	0	all	3+	3+, L. S.	0/1	4N	4 hg	4	2	0	3+	0	0	many
Bis		146	7	0	all	3+	3+, L.S.	0/0–1	0	0	0	2	0	2+	0	0	0
Jam		28	9	0	0	0	0	0/0	0	0	0	0	2+	2+	0	0	0
		1,013	37	0	few	1+	1+, L.S.	0/0	2S	0	0	0	0	1+	0	0	0
		1,234	12	0	0	0	0	0/0	0	0	0	0	0	0	0	1+	0
Win		61	13	0	all	3+	3+, L.S.	0/2	3N	3 hg	3	0	2+	2+	1+	0	few
Gar		129	13	4	all	3+	3+, L.S.	0/3–5	11N	3	3	8	0	3+	1+	0	few
Lat		122	25	0	all	3+	3+, L.S.	0/0–1	0	0	0	0	0	1+	0	0	few
Ape	6	22	15	0	all	4+	1+, L.S.	1/15–31	2N	4	4	2	4+	0	1+	±	many
		69	14	0	all	1+	1+, L.S.	0/0–1	2S	2 hg	2	4	1+	4+	0	1+	many
		307	1	0	all	2+	2+, L.S.	0/0	0	0	0	0	0	3+	0	0	few
Vla		82	10	4	all	1+	1+, L.S.	0/1–2	7S	6 hg	6	1	2+	3+	0	0	many
		162	5	1	all	1+	1+, L.S.	0/0	2S	2 hg	2	7	0	2–3+	0	0	0
Tra	5	71	15	0	all	3+	3+, L.S.	0/2	2S	1	1	2	3+	2+	0	0	many
		186	11	0	all	2+	2+, L.S.	0/1	3S	2	2	3	1+	2+	0	0	few
								Died									
Cal	7	30	16	0	all	4+	0	3/70	16N	16	16	16	4+	0	0	0	many

TABLE V

Types of glomerular lesions observed in relation to time of biopsy after onset and to clinical outcome

Days after onset	Type of glomerular lesion: Presumed focal		Primarily proliferative		Primarily proliferative with exudation or damage		Primarily exudative	
	Patient*	Outcome	Patient	Outcome	Patient	Outcome	Patient	Outcome
11					Mul	Healed		
14			Byr	Chronic				
15					Vin	Healed		
17	Ros	Healed						
20			McC	Healed				
22			Mol	Healed			Ape	Chronic
24			Eik	Healed				
27					Mar	Healed		
28	Jam†	Chronic						
30			Ser	Healed			Cal	Died
31							Lee	Healed
32	Swi	Healed	Dix	Healed				
33			San	Healed				
39			Har	Healed				
47			Roo	Healed				
61					Win	Chronic		
66			Eas	Healed			Col	Healed‡
68			Gav	Healed			(Ape	Chronic)
71			Swe	Healed	Tra	Chronic		
73			(San	Healed)				
79	(Swi	Healed)	Lar	Chronic				
80			(Ser	Healed)				
82			Dil	Healed			Vla	Chronic
97					Rob	Chronic		
114			(Mol	Healed)				
115			(Byr	Chronic)				
115			(Eas	Healed)				
120	Shi	Healed						
122			Lat	Chronic			Dra	Chronic
129					Gar	Chronic		
132			Sch	Healed				
142			Eva	Healed				
146					Bis	Chronic		
149			(San	Healed)				
156			(Ser	Healed)				
158							(Lee	Healed)
162							(Vla	Chronic)
170			Moe	Healed				
186					(Tra	Chronic)		
197							(Col	Healed‡)
205			(Mol	Healed)				
307							(Ape	Chronic)

More than one year after onset

	Glomerular lesion	Name	Outcome
602	Normal, hyalinized	(Roo	Healed)
775	Minimal proliferative	(Ser	Healed)
1,013	Normal	(Jam†	Chronic)
1,234	Normal	(Jam†	Chronic)
1,356	Miminal proliferative with glomerular damage	(Col	Healed)

* Parentheses indicate that patient had previous biopsy.
† Interstitial reaction as well as presumed focal glomerulitis.
‡ Proteinuria disappeared late (26 months after onset).

majority of patients listed as healed in the tables. Of the 23 patients who are considered to have achieved clinical cure, proteinuria persisted more than 6 months in only 4, lasting 26 months in 1 patient (Chart 1). This long duration of proteinuria is distinctly unusual among patients whose acute glomerulonephritis heals. Three patients (Dil, Eva, Mul) still had microscopic hematuria at the time of last study, but nevertheless are considered to have healed clinically. Microscopic hematuria not infrequently persists some months longer than proteinuria

in patients who eventually achieve permanent clinical healing (34).

Persistence of proteinuria for a year or more after the acute onset is considered to be reasonably good evidence for chronicity of glomerulonephritis (35) although we recognize that exceptions may occur (e.g., Patient Col). Of the 13 patients who are listed as "not healed at the time of last examination," proteinuria was documented for a year or more in 6. One patient died of hyperkalemia 32 days after onset, and undoubtedly his renal disease would have become chronic had he survived the acute phase.

The estimated time, after the onset of clinical acute glomerulonephritis, at which biopsies were obtained is given in Table III along with urine, blood urea nitrogen, and blood pressure observations at the time of each biopsy. No biopsy containing less than 5 glomeruli was included unless it was one of a series from the same patient that included one or more adequate biopsies.

Biopsy and histologic techniques. Renal biopsies were obtained by Kark and Muehrcke's percutaneous technique (36). No complications developed, except for pain at the time of actual biopsy in less than 5 per cent of the attempts. Specimens were fixed for 3 hours in Helly's solution, washed 3 hours in running water and embedded in paraffin. Sections cut at 2 and 6 μ were stained with hematoxylin and eosin (H & E), the periodic acid-Schiff (PAS) method with a hematoxylin counterstain, and Heidenhain's modification of Mallory's connective tissue stain (CT). The PAS methenamine stain of Jones (37), iron (38), hemoglobin (39), and Weigert-van Gieson stains were used when indicated. Tissue from the biopsy specimen was prepared for electron microscopy in 16 patients. For this purpose, 0.5 to 1 mm cylinders, cut from a portion of the biopsy that was believed to be cortex, were fixed in buffered osmium tetroxide which contained sucrose and dextran (40). The tissue was embedded in a 1 : 1 mixture of butyl and methyl methacrylate and then sectioned at 0.5 μ and at 0.025 μ with a Porter-Blum microtome and a glass knife. The 0.5-μ sections were stained with polychromatic methylene blue and studied by light microscopy. The thin sections were studied at 100 kv in an RCA EMU3C electron microscope.

OBSERVATIONS

I. Histopathologic changes

Data concerning the renal biopsies and the status of the patients at time of biopsy are summarized in Table III. The duration of proteinuria and of the follow-up periods are shown in Chart 1.

A summary of the histologic features of each biopsy of the 36 patients is given in Table IV. The primary changes were glomerular. Several types of glomerular lesions were noted; endothelial cell proliferation and glomerular exudation were the most characteristic. In the early stages

TABLE VI

Classification and clinical outcome of 26 patients with primarily proliferative glomerulonephritis

Classified by endothelial proliferation*	No. of patients	Clinical outcome: Healed	Clinical outcome: Chronic
Early†: Mild (1+)	4	Dix, Eik, McC, Mul	0
Moderate (2+)	5	Har, Mar, Mol, Ser, Vin	0
Marked (3–4+)	2	San	Byr
Late: Mild (1+)	3	Dil, Roo, Swe	0
Moderate (2+)	5	Eas, Eva, Gav, Moe, Sch	0
Marked (3–4+)	7	O	Bis, Gar, Lar, Lat, Rob, Tra, Win
Classified by associated exudation‡			
Early†: Focal§	3	Mar, Mul, Vin	0
Mild	4	Dix, Eik, Har	Byr
Moderate	4	McC, Mol, San, Ser	0
Late: None	9	Dil, Eas, Eva, Gav, Roo, Sch, Swe	Lar, Lat
"Glomerular damage"‖	6	Moe	Bis, Gav, Rob, Tra, Win

* Endothelial proliferation graded on the 0–4+ scale. In the late group we assume that the degree of lobular stalk hypercellularity exhibited is a reflection of the degree of proliferation that would have been present had the patient been biopsied shortly after the onset.

† Early: first biopsy obtained within 6 weeks of onset.

‡ Mild: 2–9 inflammatory cells per glomerulus; moderate: 10–20 inflammatory cells per glomerulus.

§ Focal exudation: clogging of a glomerular lobule with inflammatory cells with or without necrosis, capillary thrombosis or fibrin deposition.

‖ Glomerular damage: lobular scarring, crescents and adhesions between capillary loops and Bowman's capsule.

TABLE VII

Classification and clinical outcome of 6 patients with primarily exudative glomerulonephritis

Classified by degree of exudation*	No. of patients	Clinical outcome: Healed	Clinical outcome: Chronic
Early†: Mild	1	Lee	0
Moderate	1	0	Ape
Marked	1	0	Cal (died)
Late: Glomerular damage	3	Col	Dra, Vla
Classified by associated endothelial proliferation			
Early†: None	1	0	Cal (died)
Mild (1+)	2	Lee	Ape
Late: Mild (1+)	2	0	Dra, Vla
Moderate (2+)	1	Col	0

* Degree of exudation based on number of inflammatory cells in glomeruli, but all patients also had crescents, adhesions and other glomerular damage which are difficult to quantitate.

† First biopsy obtained within 6 weeks of onset.

endothelial proliferation generally was diffusely distributed within capillary loops. Later the hypercellularity was more focal and located in the "stalks" of each glomerular lobule. The exudative reaction, the acute stages of which rarely extended beyond 6 weeks, was characterized by an increased number of polymorphonuclear leukocytes within the glomerular capillary loops. Diffuse and focal distributions of the leukocytes were noted with almost equal frequency. Other evidence of glomerular injury included lobular necroses or scars, epithelial cell crescents and adhesions between glomerular lobules and epithelial cell crescents or Bowman's capsule; capillary loop thrombi were seen in 2 patients. Such evidences of glomerular injury with rare exceptions exhibited focal distribution. In several parts of the text and in several tables these lesions have been grouped together, for convenience, under the term *glomerular damage.*

The patients were grouped by an arbitrary system based on the predominant glomerular lesions noted in their renal biopsies (Table V). Three patients were classified as *presumed focal glomerulitis,* 1 as *presumed focal glomerulitis and interstitial reaction,* 18 as *primarily proliferative,* 8 as *primarily proliferative with glomerular damage,* and 6 as *primarily exudative.* Leukocytic infiltration, the most characteristic feature of the exudative process, was rare after 6 weeks, and, when present after 6 weeks, was minimal. However, of the 25 patients first biopsied more than 6 weeks after onset, 3 (Col, Vla, Dra) were classified arbitrarily as primarily exudative on the basis of prominent glomerular scarring and only mild proliferative changes. The glomerular changes in these 3 patients were very similar to those noted in Ape and Lee, whose earlier biopsies revealed unequivocal exudative reactions. Proliferative changes were more marked, and scars, adhesions and crescents less marked and more focal, in the 8 patients classified as primarily proliferative with glomerular damage. Five biopsies were obtained from 4 of the patients more than 1 year after onset. The classifications of the 36 patients are summarized in several different ways in Tables V, VI and VII. Reference to these tables will assist in orienting the reader in several parts of the text.

1. Acute proliferative glomerulonephritis. The predominant glomerular lesion in 26 patients (Tables IV–VI) was an increased number of endothelial cells within the glomerular capillary loops of all unhyalinized glomeruli (Figures 1–12). This glomerular response, which corresponds to classic acute proliferative glomerulonephritis, was the most characteristic feature of our patients with proved post-streptococcal acute glomerulonephritis. The extent of the endothelial proliferation was variable, although in each of these 26 patients all glomeruli were involved to some degree.

Eleven patients were biopsied in the early phase of the proliferative response (first 6 weeks after onset). Three additional patients (Mar, Mul, Vin) had diffuse endothelial proliferation complicated by considerable focal exudation. Most of the new endothelial cells had vesicular nuclei which appeared larger and paler than those of normal endothelial cells (Figures 2, 4, 9, 12). Their cytoplasm was pale, stained lightly with both eosin and azocarmine, and was only slightly positive to the PAS reaction. Small hyaline fibers, which stained blue with Heidenhain's stain, or brownish black with the PAS-methenamine stain, were prominent in the cytoplasm of the endothelial cells, especially in areas of marked hypercellularity (Figures 7, 12).

The degree of hypercellularity varied considerably from patient to patient, ranging from about 1.5 to 3.5 times normal. The mildest proliferative changes were noted in Mul, Dix, Eik and McC

(Figures 10, 11), and should be contrasted with the more marked proliferation exhibited in some glomeruli in Byr (Figure 5) and in almost all of the glomeruli of San (Figures 1, 2, 12). The new cells were usually found in small clusters in a central position in the lobules of the glomerulus in the mild cases, but completely filled many of the lobules in patients with marked proliferative response. The capillary loops seemed to be completely occluded in the areas of marked proliferation (Figures 1, 2, 5, 12) but were usually widely patent in the mild cases, particularly those at the periphery of the lobules (Figures 10, 11).

The degree of hypercellularity also varied among different glomeruli in the same biopsy. This appeared clearly in Byr, some glomeruli showing a marked proliferative response, and others much less severe changes (Figure 5). In addition, different lobules within a single glomerulus frequently varied considerably in degree of involvement. Ser, Byr and Mol all showed this variation (Figures 3, 6, 9).

Careful search of thin sections of glomeruli in the patients in the early phases of acute proliferative glomerulonephritis revealed mitotic figures in Byr and San. Some of the mitoses are shown in Figures 1, 2 and 8. The mitoses always occurred in cells that were located within and attached to the glomerular capillary basement membrane (endothelial cells). San had as many as three mitoses per 2μ section of glomerulus.

All 11 patients with proliferative acute glomerulonephritis studied within 6 weeks of onset exhibited some increase in the number of polymorphonuclear neutrophiles within capillary loops, although the increase was minimal (5 or less per glomerulus) in 4 patients. In all instances the number of intraglomerular leukocytes noted in the proliferative group was less than that noted during the acute phase of the exudative response, when as many as 75 polymorphonuclear neutrophiles were observed within a single glomerulus (*vide infra*). Eosinophilic polymorphonuclear leukocytes were noted in addition to the neutrophiles in 5 patients in the proliferative group. The significance of the eosinophilia is not known. Eosinophiles were not noted in later biopsies from these patients, nor was significant eosinophilia in the circulating blood demonstrated in any. The leukocytes were diffusely distributed throughout the glomerular capillary loops in 7 patients. In 3 (Mar, Mul, Vin) the exudative process was focal in distribution. For instance, several lobules in Vin's biopsy contained as many as 15 neutrophiles. Other entire glomeruli contained only a third of this number of leukocytes. Similar findings are illustrated in the biopsy shown in Figure 29 (Mar), where the lobule at 8 o'clock contains 22 leukocytes.

Evidences of glomerular damage (lobular necrosis or scars, crescents, adhesions or capillary thrombi) were noted in 5 of the 11 patients in the early proliferative group. More than 20 per cent of the glomeruli were involved in only 2 of these. One (Mar) had focal exudation. The other (McC) was a 59 year old male who had significant arterio- and arteriolar nephrosclerosis that probably were responsible for the 11 hyalinized glomeruli among the total of 15 in the biopsy. Two of the patients (Mar, Mul), biopsied within 4 weeks of onset, had occasional thrombi in capillary loops (Figure 29).

Few abnormalities were noted in the glomerular epithelial cells in the early primarily proliferative group except in 2 patients (Byr, McC) in whom crescents were present (Figure 8). One crescent in Byr contained a mitotic figure. The cytoplasm of some of the epithelial cells covering the capillary loops contained hyaline droplets that stained with azocarmine and were positive to the PAS reaction (Figures 6, 8). Similar droplets were common in the cytoplasm of the proximal tubular cells in these patients.

The basement membranes of the peripheral glomerular capillary loops of the unhyalinized glomeruli were normal in all patients in the early primarily proliferative group. Small foci of periglomerular edema and early interstitial fibrosis were noted in 8 of the 11 patients in the group. These foci usually contained a few atrophic tubules. Patient McC had rather severe interstitial fibrosis. Some of this was of recent origin, but much apparently was the result of long-standing vascular disease. The lack of over-all acute disruption of cortical architecture in this group was striking, especially when compared with the findings in the primarily exudative group (Patients Ape and Cal).

The histologic changes in subsiding acute proliferative glomerulonephritis of moderate or marked

severity (from 6 weeks to 7 months after onset) are illustrated by subsequent biopsies in 4 of the proliferative cases (Ser, Byr, San, Mol). Glomerular hypercellularity was still present, but the pattern had shifted from a generally diffuse to a more focal distribution. The hypercellularity was now the result of a collection of cells in the stalks of each glomerular lobule (Figures 14–26). The nuclei of the cells in the hypercellular foci were more basophilic and less vesicular than the average endothelial cell nucleus noted in the acute stage. Their cytoplasm was eosinophilic, positive to the PAS reaction, and stained blue with aniline blue. Cellular borders were not present, and small, linear, irregular hyaline intracytoplasmic fibers that stained a bright refractile blue with aniline blue, with much the same intensity and coloration as basement membrane, were readily seen in thin sections (Figure 13). These fibers had some of the staining reactions of collagen. However, they did not stain with silver except after prior oxidation with periodic acid (Figure 26). Also, these fibers did not show the typical periodicity of collagen in electron micrographs of the biopsy obtained 215 days after onset in Mol (Figures 27, 28).

Similar lobular stalk hypercellularity was observed in the glomeruli of the patients in the proliferative group who were biopsied for the first time 6 weeks or more after onset. The degree of hypercellularity varied considerably (Figures 30–37). Some glomeruli were more hypercellular than others in the same biopsy, and frequently some lobules within a single glomerulus were more hypercellular than others (Figure 34). The actual number of cells within the lobular stalks probably was directly related to the degree of proliferation present during the acute phase.

Exudative changes, particularly those of the focal type, that are of sufficient severity to lead to scarring (e.g., Mar, Vin, Mul) or are manifest later by lobular scarring, are a prominent variable relating to the severity of any given attack of glomerulonephritis. This generalization can best be demonstrated by contrasting the course of Patient San (Case 4, Figures 1, 12, 21, 22), who had relatively pure marked proliferative glomerulonephritis without glomerular damage and interstitial scarring, with the course of Patient Tra (Case 5, Figures 63, 64), who exhibited signs of marked initial proliferation—namely, striking lobular stalk hypercellularity, plus lobular scars, adhesions and severe interstitial fibrosis. Tra's histopathologic findings apparently are the result of an initial mixed proliferative and exudative response. Very similar changes were shown by Rob (Figures 53–55), Gar and Win. They also are believed to be the result of an initial mixed proliferative and exudative response.

Only 2 patients (Ser, Gar) showed signs of active acute glomerular inflammation more than 6 weeks after onset. Glomeruli in a biopsy obtained 129 days after onset in Gar contained 3 to 5 polymorphonuclear leukocytes per glomerulus in the 2μ sections. Occasional deposits of fibrinoid in the capillary loops and lobular stalks also were present. A few capillary basement membranes in most glomeruli were thickened, the only instance of thickened basement membranes in significant numbers in our entire series. Occasional glomerular endothelial cells with abundant finely vacuolated cytoplasm, presumably filled with fat droplets, also were noted. The cytoplasm of some of the proximal tubules contained multiple small cytoplasmic vacuoles which were likewise presumably fat. Cases 1 through 5 in the protocols illustrate the proliferative group.

Biopsies were obtained more than a year after the onset in only 2 patients in the proliferative group. Roo, who had mild hypercellularity initially, showed no recognizable signs of antecedent glomerular disease (Figure 38) in a biopsy taken 602 days after the onset and 249 days after disappearance of proteinuria (Figure 39). Ser, who had moderate hypercellularity initially, showed very minimal lobular stalk thickening without much hypercellularity in 1 of 2 glomeruli obtained in a biopsy 26 months after the onset (Figure 18).

2. Primarily exudative glomerulonephritis. All 3 patients, so classified and biopsied within 6 weeks of onset, showed marked increases in the number of polymorphonuclear neutrophiles within the glomeruli. Endothelial cell proliferation, although present, in Ape and Lee was not a prominent feature (Figure 41). No evidence of endothelial proliferation was noted in Cal. The diagnosis of exudative glomerulonephritis can be made objectively only during the early phases of the dis-

ease. After the leukocytes have disappeared, usually 50 to 60 days after onset, it is impossible to be certain that the initial disease was primarily exudative in character.

Ape, Lee and Cal, in addition to infiltration of the glomeruli with polymorphonuclear leukocytes also exhibited glomeruli with adhesions (Figures 42, 43, 45, 46), lobular necrosis (Figures 42, 43), and crescents (Figures 42, 45, 46). The cortical tissue was edematous (Figures 40, 45). Many proximal tubules were lined by regenerating or flattened epithelium. Later biopsies from Ape showed diffuse and marked interstitial fibrosis (Figures 48, 49). The second biopsy obtained 69 days after onset had 0 to 1 neutrophiles per 2μ section of glomerulus and very slight lobular stalk hypercellularity (Figure 49). Some glomeruli also showed lobular scars and adhesions (Figure 50). Her third biopsy, 307 days after onset, contained a single glomerulus which showed severe disease. It was adjacent to an area of marked juxtamedullary cortical inflammation and fibrosis. Lee's second biopsy, 158 days after onset, showed glomerular lobular scars, slight lobular stalk hypercellularity and considerable focal interstitial fibrosis.

Few changes in glomerular ultrastructure were observed by electron microscopy in the portions of glomeruli lacking crescents in the biopsy on Cal. The basement membranes and the foot processes of the epithelial cells over the basement membranes were normal (Figure 47). Endothelial cell proliferation was absent. The cytoplasm of the endothelial cells formed a thicker layer than is usually observed in glomeruli, and numerous polymorphonuclear neutrophiles were present in the capillary loops, apparently adherent to the cytoplasm of the endothelial cells. Case histories of Ape and Cal are given in the protocols (Cases 6 and 7) and should be contrasted with Cases 1–5.

Patients Col (Case 8, Figures 51, 52, 56, 57), Vla (Figures 58–62), and Dra were considered to be examples of primarily exudative glomerulonephritis (Tables V, VII). The first biopsies in these patients were not obtained until 2 to 4 months after onset, at a time when the glomerular leukocytic infiltration would be expected to have disappeared and the acute exudative lesions to be healed or healing. Occasional glomeruli in each patient showed mild lobular stalk hypercellularity, indicating that some initial proliferative disease had been present. The extensive glomerular scarring and interstitial fibrosis in the absence of marked proliferation, and the similarity of the biopsies to the changes noted in late biopsies on Ape and Lee, led to our arbitrary decision to place these 3 patients in the exudative group.

3. Presumed focal glomerulitis. Patients Ros, Swi (Case 9 in protocols) and Shi (Case 10) comprise this group (Tables IV, V). Focal and very slight lobular stalk hypercellularity was present in most glomeruli in Shi's biopsy, obtained 120 days after onset (Figure 65). One glomerulus showed a lobular scar adherent to a small healing crescent (Figure 66). Biopsies obtained in all other patients with subsiding proliferative glomerulonephritis, at about the same time after onset as in Shi, revealed diffuse glomerular involvement. Although unusual in post-streptococcal glomerulonephritis, focal glomerular lesions similar to Shi's may have been present in Ros and Swi, but were not included in the small samples of glomeruli obtained by biopsy. This situation has been reasonably well established in an outbreak of nonstreptococcal acute nephritis (22). Significant glomerular lesions were not noted in either Ros or Swi, even though biopsies were obtained 32 and 17 days, respectively, after onset (Figures 67, 68). Alternatively, minor lesions not detectable by light microscopy could have accounted for the urinary abnormalities in Ros and Swi.

4. Interstitial reaction, presumed focal glomerulitis. Jam developed unequivocable laboratory evidence of acute glomerulonephritis 14 days after acute tonsillitis due to a Type 12 streptococcus. His history has been given in detail [Case 1 (24)]. During a long follow-up period (40 months) he exhibited persistent 1 + proteinuria and a labile hypertension. The first biopsy, obtained 28 days after onset, is illustrated in Figures 69 and 70. No overt glomerular lesions were present. The only unusual findings in the first biopsy were two tiny foci of interstitial edema, fibrosis, minimal chronic inflammatory cell infiltration and tubular atrophy. No organisms were identified in the sections, and cultures of the blood in the biopsy needle were sterile. Subsequent biopsies from this patient (Figure 71) up to 40 months after

onset of clinical disease showed no further changes, even though proteinuria persisted and mild hypertension developed. Electron micrographs of the last two biopsies showed normal glomerular ultrastructure. The last biopsy exhibited a few sclerotic arterioles. Whether the continued proteinuria resulted from a chronic glomerulonephritis not detectable on biopsy or from nephrosclerosis is not clear. The latter possibility seems the more likely in view of the absence of glomerular changes. Nevertheless, he is listed as chronic glomerulonephritis in the tables.

5. Tubular and interstitial changes. The cytoplasm of the proximal tubules of all patients who had proteinuria at the time of biopsy (Table III) contained some hyaline droplets that stained with azocarmine and were PAS-positive. Although erythrocytes were uncommon in Bowman's space, they were frequently noted in the lumens of the proximal tubules during the acute phase of the disease. Red blood cell casts, heme casts or granular casts containing erythrocytes were noted in 17 of the 36 patients, especially in the first 6 to 8 weeks of illness. Hyaline casts were uncommon except in the older patients or in patients who had considerable interstitial fibrosis.

Small scattered foci of interstitial fibrosis were noted in 11 of the 36 patients; moderate to severe interstitial fibrosis was noted in 17. With the exception of Jam, all patients with moderate to severe interstitial fibrosis also had evidence of moderate to marked proliferative or exudative glomerular disease. On the other hand, 4 patients (San, Lar, Lat, Byr) with marked proliferative disease had little or no interstitial reaction.

6. Vascular disease. No acute arteriolar disease with necrosis or fibrinoid was noted in any of the 36 patients; 11 did show eccentric subintimal hyaline deposits in the walls of arterioles. The arteriolar lesions were usually minimal in extent except in Roo, Eik and McC, who showed sufficient associated old interstitial fibrosis to be classified as arteriolar nephrosclerosis. The hyalinized glomeruli in McC probably were the result of the vascular disease. Curiously, the glomerulonephritis in these 3 patients was mild histologically, and healed by clinical standards. Fibrous arteriosclerosis was noted in one or more arteries in 8 patients, 3 of whom did not show associated arteriolar disease.

II. Relationship of biopsy findings to clinical course

The degree of proteinuria and hematuria noted at the onset of acute glomerulonephritis in all patients is given in Table II, along with the results of the last available urinalysis. Clinical healing occurred in the first 23 patients in Tables I and II and Chart 1. Proteinuria disappeared in 3 months or less in 14 patients, and in less than 6 months in 19; Col was the only patient in whom proteinuria is known to have disappeared later than 1 year after onset. Proteinuria in Patient Moe disappeared some time between 8 and 24 months after onset.

Among 13 patients who still had proteinuria at the time of last observation, the follow-up period exceeded 12 months in 6. That the remaining 7 patients have developed chronic glomerulonephritis, therefore, is not certain, although proteinuria has been documented for 5 months or more in all but 4. Nevertheless, certain observations suggest that several of the patients with relatively short follow-ups will, in fact, develop chronic glomerulonephritis. Heavy proteinuria was still present in Patients Dra and Byr at 10 and at 4.5 months, respectively. Patient Rob still had many erythrocytes in his urinary sediment and a 1 + proteinuria 4 months after onset. Unfortunately, he was killed in an accident 1 year after onset. Patient Cal died 32 days after onset, despite several dialyses on the artificial kidney. Had he survived the acute episode, he undoubtedly would have developed chronic glomerulonephritis or died from subacute disease.

For these reasons and for the purposes of the present paper, we will consider that all 13 patients who had proteinuria at the time of last examination are examples of the development of chronic glomerulonephritis following an attack of post-streptococcal acute glomerulonephritis. We recognize, however, that our judgment may be erroneous in several instances. Murphy and Schulz (10) and Richter (35) report that glomerulonephritis rarely healed clinically more than 1 year after onset.

1. Histologic findings and outcome of acute glomerulonephritis. Certain histologic features that might be related to the outcome of acute glomerulonephritis are presented in Tables V–IX. Some of the details of the histologic features used in

TABLE VIII

*Certain histologic findings and clinical outcome in patients with acute glomerulonephritis, grouped according to predominant lesions**

Patient	No. of glom.	Endothelial prolif.†	Leukocytes per glom.	No. of glom. with damage‡	Interstitial reaction§	Clinical outcome
		Presumed focal glomerulitis				
Ros	14	0	0	0	0	Healed
Swi	8	0	0–1	0	0	Healed
Shi	17	±, L.S.	0	12	1+	Healed
		Interstitial reaction, presumed focal glomerulitis				
Jam	9	0	0	0	2+	Chronic
		Primarily proliferative; early (within 6 weeks of onset), including focal exudation				
Eik	10	1+, L.S.	5	0	0	Healed
Dix	25	1+, L.S.	4	4	0	Healed
Mul	9	1+, Dif.	7–24	12	2+	Healed
McC	15	1+, L.S.	11	100	3+	Healed
Ser	6	2+, Dif.	13	0	1+	Healed
Vin	5	2+, Dif.	5–22	0	1+	Healed
Mol	10	2+, Dif.	12	0	1+	Healed
Har	15	2+, L.S.	1–6	0	2+	Healed
Mar	5	2+, Dif.	14–30	20	2+	Healed
San	7	3+, Dif.	9	0	0	Healed
Byr	20	2–4+, Dif.	2	15	1+	Chronic
		Primarily proliferative; late (6 weeks to 1 year after onset)				
Swe	17	1+, L.S.	0–1	0	0	Healed
Roo	10	1+, L.S.	1–2	0	1+	Healed
Dil	22	1+, L.S.	1	5	1+	Healed
Sch	36	2+, L.S.	0–1	0	0	Healed
Gav	13	2+, L.S.	0–1	0	1+	Healed
Eva	13	2+, L.S.	0–1	0	1+	Healed
Eas	11	2+, L.S.	0–1	0	1+	Healed
Moe	19	2+, L.S.	0–1	5	2+	Healed
Lar	35	3+, L.S.	0–1	0	0	Chronic
Lat	25	3+, L.S.	0–1	0	1+	Chronic
		Primarily proliferative with glomerular damage (late group only)				
Bis	7	3+, L.S.	0–1	29	2+	Chronic
Tra	15	3+, L.S.	2	33	3+	Chronic
Win	13	3+, L.S.	2	30	2+	Chronic
Gar	13	3+, L.S.	3–5	85	3+	Chronic
Rob	6	3+, L.S.	1	100	3+	Chronic
		Primarily exudative; early (within 6 weeks of onset)				
Cal	16	0	70	100	4+	Died
Ape	15	1+, L.S.	15–31	33	4+	Chronic
Lee	16	1+, L.S.	3–9	56	2+	Healed
		Primarily exudative; late (6 weeks to 1 year after onset)				
Vla	10	1+, L.S.	1–2	70	3+	Chronic
Dra	19	1+, L.S.	0–1	90	3+	Chronic
Col	12	2+, L.S.	2–3	67	2+	Healed (late)

* Only first biopsy included when more than one was obtained in a given patient. Within each group patients are arranged in relation to degree of endothelial cell proliferation.

† Endothelial cell proliferation on 0–4+ scale; location of endothelial proliferation: L.S. = lobular stalk. Dif. = diffuse.

‡ Glomerular damage = lobular necrosis or scar, capillary loop thrombus, crescent, adhesion or hyalinization.

§ 0 = no fibrosis, edema or inflammatory cells; 1+ = occasional tiny periglomerular foci; 2+ = larger cortical areas involved; 3+ = 50% or more of cortex involved; 4+ = diffuse edema or fibrosis. The interstitial reaction in all patients in the "early" group was recent except in McC who had both recent and healed fibrosis. In the "late" group the interstitial fibrosis was healed except in Col, Tra, Vla and Win in whom mixtures of recent and healed interstitial reactions were noted.

this analysis are given in Table VIII. Within each classification in this table, the patients are listed in order of increasing degrees of endothelial cell proliferation, and within each degree-of-proliferation group they are listed in order of increasing degrees of "glomerular damage." Glomerular hypercellularity and endothelial cell proliferation were graded on a scale of 0 to 4 +. When glomerular leukocytes were distributed diffusely, a single figure was given to indicate the mean number of leukocytes per glomerulus. When the exudative process was focally distributed, the range of leukocytes per glomerulus was given. The percentage of total glomeruli in the biopsy that exhibited thrombi or scars, adhesions, crescents or hyalinization was given to indicate the extent of "glomerular damage." Interstitial reaction was graded on a scale of 0 to 4 +.

The histological findings in Table VIII can be analyzed singly or together. We believe that the most useful analysis of the relation of histologic changes to the outcome of acute glomerulonephritis is based on the predominant type of lesion. Accordingly, the outcome in our 36 patients has been analyzed with respect to the severity of glomerular endothelial proliferation, exudation and "damage," and of the interstitial reaction (Tables VI, VII, IX).

TABLE IX

Relation of severity of certain histologic lesions to outcome of acute glomerulonephritis

Lesion	Severity	Clinical outcome*	
		Healed	Chronic
Endothelial cell proliferation†	0–2+	22	3
	3–4+	1	8
Glomerular damage‡	0–25%	20	4
	>25%	3	7
Interstitial reaction†	0–2+	21	4
	3–4+	2	7
Average of above§	0–2+	20	3
	3–4+	3	8

* Patients Jam, who had an unusual lesion (interstitial reaction, presumed focal glomerulitis) and who probably developed essential hypertension, and Cal, who died 32 days after onset, are excluded from this analysis.

† Severity recorded as designated in Table VIII.

‡ Per cent of glomeruli involved.

§ For purposes of calculating this average the severity of glomerular damage was assigned as follows: no glomerular damage, 0; 1–12% glomeruli involved, 1+; 13–25% involved, 2+; 26–49% involved, 3+; >49% involved, 4+.

The three patients classified as *presumed focal glomerulitis* all had rather mild clinical acute glomerulonephritis, had little or no evidence of endothelial cell proliferation, and healed, although proteinuria persisted for 9.5 months in Swi. Healing in this group was not unexpected, judging from the paucity of pathologic change observed in their biopsies. Glomerulonephritis in Swi and Ros was a "laboratory diagnosis" made on the basis of urinalyses done because of pharyngitis. Perhaps the renal lesions in these patients were similar to those in the majority of patients in epidemics such as that described by Stetson and co-workers (28). However, histologic studies in a large group of patients with mild, clinical, proven poststreptococcal glomerulonephritis, both epidemic and sporadic, will be required before much further knowledge will be gained about this type of renal response.

Patient Jam, who had interstitial reaction and presumed focal glomerulitis, apparently failed to heal, although continued evidences of renal disease could have been due to renal vascular disease and nephrosclerosis, rather than to glomerulonephritis. He was excluded from further consideration in this analysis.

Fourteen of the remaining 32 patients were biopsied within 6 weeks of onset. Eleven of the 14 (Tables V, VI) were classified as *primarily proliferative, with or without glomerular damage,* and only one of these failed to heal. The initial biopsy on this patient (Byr) showed some markedly hypercellular glomeruli (Figure 5) while others were only moderately hypercellular. The only other patient with marked proliferative glomerulonephritis who was studied early healed 4 months after onset (San, Figure 12). Mild or moderate degrees of hypercellularity were exhibited by the other 9 patients, all of whom healed regardless of the amount of glomerular damage (Table VIII).

Fifteen of the patients (Tables VI, VIII), first biopsied more than 6 weeks after onset, were classified as examples of *proliferative glomerulonephritis, with or without glomerular damage; 7* of these failed to heal. All 7 had evidence of marked (3 to 4 +) endothelial proliferation (Figures 13, 32, 33, 35, 55, 63). The disease healed clinically in the remaining 8 patients who had

mild (1 +) or moderate (2 +) endothelial proliferation. The same 15 patients were reclassified in relation to the degree of observed glomerular damage rather than the degree of proliferation (Table VI). Clinical healing was achieved in 7 of the 9 patients who had little or no evidence of glomerular damage or interstitial reaction (Figures 30, 34, 38). The disease healed in only 1 (Moe) of the 6 patients who had glomerular damage in more than 20 per cent of their glomeruli. The histologic picture in the patients with chronic disease in the primarily proliferative group is one of marked lobular stalk hypercellularity and varying amounts of glomerular scarring. Bell, who first described this lesion, named it *chronic latent glomerulonephritis* (65).

Six patients were classified as *primarily exudative* (Table VIII). Three patients (Cal, Ape, Lee) were biopsied within 6 weeks of onset. Cal (Case 7), who had no evidence of endothelial cell proliferation, but did have very extensive glomerular damage and interstitial reaction, died 32 days after onset. Autopsy confirmed the biopsy findings. Ape (Case 6), who had marked but less severe glomerular damage, also had some slight endothelial proliferation. She slowly improved clinically but still had evidence of chronic glomerulonephritis 25 months after onset. Lee's first biopsy exhibited mild diffuse exudation, crescents and necrotic glomerular lobules in about one-third of the glomeruli, along with evidence of slight endothelial proliferation. His proteinuria disappeared 2 months after onset.

The remaining 3 patients (Vla, Col, Dra), who were first biopsied more than 6 weeks after onset, have been classified in Table VIII as late examples of *primarily exudative glomerulonephritis.* They all had extensive glomerular damage, interstitial fibrosis and evidence of mild (1 +) or, in one case, moderate (2 +) endothelial proliferation. The histologic pattern noted in these 3 patients was similar to that observed in the later biopsies on Ape. Placement of these 3 patients in the exudative group is arbitrary, since there is no objective criterion at this late date, aside from the observed extensive glomerular and interstitial scarring, to prove the initial disease was exudative in character. Two of the 3 patients have persistent proteinuria, while the clinical disease in one (Col) healed late (26 months after onset). The histologic pattern of the unscarred glomeruli in these patients is quite different from the 8 examples of chronic disease discussed earlier in Table VI.

TABLE X

Relation between over-all severity of renal lesion and several clinical features of acute glomerulonephritis *

Severity of renal lesion	Patient	Max. BUN	Max. diastolic blood pressure	Edema
		mg %	*mm Hg*	
0–1+	Swi	12	60	0
	Dil	14	84	0
	Ros	15	70	0
	Shi	17	80	0
	Swe	20	90	0
	Jam	25	90	0
	Roo	27	90	3+
2+	Sch	15	100	0
	Gav	18	80	1+
	Eas	20	100	0
	Dix	24	95	0
	Mul	24	100	2+
	Moe	25	120	0
	Har	25	108	3+
	Eva	33	90	0
	Eik	35	110	4+
3+	Dra	15†	85	2+
	Byr	17	80	0
	Ser	22	116	3+
	Lar	22†	120	1+
	Mol	24	60	0
	Bis	24†	110	2+
	Vin	25	116	2+
	Col	28†	118	3+
	McC	45	110	2+
	Lat	45	98	2+
	Lee	66	86	3+
	Mar	128	95	2+
4+	Rob	24†	120	3+
	Win	39	110	4+
	Gav	40	120	1+
	San	42	110	1+
	Ape	79	130	4+
	Vla	95	100	3+
	Col	179	116	4+
	Tra	200	98	0

* In this analysis the over-all severity of the renal lesion on a scale of 0 to 4+ is estimated from the degree of obstruction of the glomerular capillaries by endothelial cell proliferation and leukocytes, the amount of glomerular damage and the severity of the interstitial reaction.

† First blood urea nitrogen obtained more than 2 weeks after onset.

The over-all relationship of the histologic findings to the outcome of acute glomerulonephritis in 34 patients [1] is summarized in Table IX. It is ap-

[1] Patients Jam, who had an unusual lesion (interstitial reaction, presumed focal glomerulitis) and who probably

TABLE XI

Relation between several clinical features and clinical outcome of acute glomerulonephritis

	Clinical outcome	
	Healed	Chronic
Blood urea nitrogen (mg%)		
–19	6	2
20–29	11	4
30–49	4	3
50–	2	4
Diastolic blood pressure (mm Hg)		
–94	10	3
95–	13	10
Edema		
Absent	11	3
Present	12	10

parent that a relationship exists between the degree of endothelial proliferation and the incidence of chronicity. Eight of 9 patients with 3 to 4 + hypercellularity still have persistent proteinuria, while only 3 of 22 with mild and moderate degrees of endothelial proliferation have signs of chronic disease. The three exceptions (Ape, Dra, Vla, in the mild proliferative group and whose diseases failed to heal) all had had a primarily exudative reaction and considerable glomerular damage. The clinical disease healed in the three patients without diffuse endothelial proliferation. The relationship between the severity of "glomerular damage" and interstitial reaction and chronicity also was reasonably good, but more exceptions were noted.

Five patients (Col, Har, Mar, Tra, Vla) were treated with steroid hormones. At the time of treatment Tra was critically ill with severe uremic symptoms, while Vla and Mar had marked nitrogen retention and other clinical evidence of severe renal disease. Shortly after institution of steroid therapy all five patients began to show evidence of improvement. Although this improvement was rather dramatic in Tra, Vla and Mar, we are not yet prepared to state that steroids were responsible, since improvement often occurs spontaneously in severe acute glomerulonephritis.

developed essential hypertension, and Cal, who died 32 days after onset, are excluded from this analysis.

2. Histologic and clinical findings. An attempt was made to estimate from histologic evidence the reduction to be expected in glomerular filtration rate. The histologic estimations, graded on a scale of 0 to 4 +, are summarized in Table X in relation to the incidence of nitrogen retention, diastolic blood pressure and edema. In general, a reasonably good relationship between the estimated severity of glomerular lesions and the blood urea nitrogen (BUN) level was observed, although there were some impressive exceptions, several of which had reasonable explanations. For instance, in the 0 to 1 + glomerular damage group, Patients Jam and Roo, whose BUN levels were slightly increased, had relatively marked interstitial fibrosis. In addition, some glomeruli in Roo's biopsy were completely hyalinized, presumably the result of vascular nephrosclerosis. In the 3 and 4 + groups, the BUN recorded for Dra, Lar and Rob was not obtained during the first 2 weeks of their disease. Diastolic hypertension was more common among the patients with the severe glomerular damage, but again notable exceptions were apparent, as was the case with edema.

Byr and Mol represent important exceptions. Their clinical symptoms were mild, hypertension and edema did not develop, and renal functional impairment was minimal. Nevertheless, both had significant glomerular hypercellularity. The disease failed to heal in Byr.

3. Clinical findings and outcome of acute glomerulonephritis. The relationship of blood urea nitrogen levels, diastolic hypertension and edema to the outcome of acute glomerulonephritis is shown in Table XI. Again, in general, the more severe the clinical findings the less likely was acute glomerulonephritis to be followed by healing. However, exceptions were numerous and obvious.

DISCUSSION

The patients reported in this paper had sporadic acute glomerulonephritis following an infection proved to be due to a Group A hemolytic streptococcus organism. Distinctive renal lesions were observed in 32 of the 36 patients. No distinctive histologic lesions were noted in 4 patients whose diagnosis rested entirely on laboratory findings.

The fate of the pathologic changes in many of the patients in this series is still unknown. Such information will not be available until they have been followed for a longer time. Thus, some of our present conclusions about the natural history of acute post-streptococcal glomerulonephritis are subject to the restrictions of limited follow-up.

The pathology of fatal acute glomerulonephritis has been thoroughly documented. The present report is unique only in that it is a study of nonfatal cases, and that our cases have been restricted on etiologic grounds to those associated with proved streptococcal infection. The recent reports of Hutt, Pinniger and de Wardener (20), Howe (15), and Brun and co-workers (67) on smaller series of nonfatal cases certainly included some cases of post-streptococcal glomerulonephritis. However, interpretation of their reports in relation to our findings is difficult because of the lack of etiologic discrimination.

Langhans (1), Welch (41), Reichel (42), Löhlein (2) and a number of other early authors all demonstrated that the basic lesion in most fatal cases of acute glomerulonephritis was an increase in the number of cells within the glomerular capillary loops. Our observations are generally similar. It is noteworthy that these early workers observed most of the significant changes now considered to be characteristic of this disease. The main differences between their cases and ours are those of degree.

Clinical glomerulonephritis varies considerably in severity. The range of histologic damage in our series also has varied from no observable disease by light microscopy to marked acute proliferative or exudative glomerulonephritis. An endothelial proliferative response is most common; 30 of our 36 nonfatal cases showed this response, as did 57 of Bell's group of 60 fatal cases (43). No doubt most cases of acute diffuse proliferative glomerulonephritis reported in the literature are post-streptococcal in etiology. This association has been documented in most recent studies (8, 26–28, 44, 45), and has, in fact, been loosely documented in the older literature, particularly in those papers reporting classic intracapillary glomerulonephritis following scarlet fever [Langhans, 1885 (1), Löhlein, 1907 (2), and Volhard and Fahr, 1914 (3)]. Reichel in 1905 (42), even entitled his classic paper on acute glomerulonephritis, "Über Nephritis bei Scharlach." [2]

Nature of the glomerular changes. The term *proliferative* in relation to the increase in mononuclear cells within the basement membranes of the glomerular capillary loops has been questioned by MacCallum (46), Jones (47) and Grishman and Churg (48). MacCallum theorized that no real reason existed for assuming that inflammation in the glomerulus should differ from inflammation elsewhere in the body. He decided, on morphologic grounds, that the hypercellularity of acute glomerulonephritis was due to mononuclear cell infiltration into the glomerular capillary loops. We noted mitosis in cells inside and attached to the glomerular capillary basement membrane (by definition, endothelial cells) during the early phase of the clinical disease in 2 patients. This is strong evidence against MacCallum's theory. We are not alone in this observation, since mitoses have been noted previously by a number of workers (5–7, 49, 50). Furthermore, mitoses are commonly observed in capillary endothelial cells in the initial phases of "Masugi" antikidney serum nephritis in the rat (51).

Farquhar, Vernier and Good's (17) electron micrographs of hypercellular glomeruli from the initial phases of acute proliferative glomerulonephritis and our micrographs (Figures 27, 28) of diseased glomeruli from the subsiding phase show cells with characteristic cytoplasmic inclusions of material with the same morphologic qualities and electron density as glomerular capillary basement membrane. Such inclusions have never been reported in mononuclear inflammatory cells. It seems clear from these observations and arguments that good evidence exists to indicate that *proliferative* is a valid term descriptive of the phenomena occurring in this disease.

Two patients in our series showed marked glomerular hypercellularity, which was primarily due to an increase in the number of polymorphonuclear neutrophiles within the glomeruli. Minimal endothelial cell proliferation was present in 1 patient, but was overshadowed by the exudative response. Glomerular necrosis, crescents, and other signs of severe renal disease were common in these pa-

[2] See Reichel's paper for a list of 12 earlier papers on *Scharlachnephritis.*

tients but also occurred in patients with the primarily proliferative disease. Severe acute exudative glomerulonephritis, as observed in Cal, is very similar to the extracapillary glomerulonephritis described first by Langhans in 1885 (1). We suspect that acute exudative glomerulonephritis is the antecedent lesion of so-called subacute glomerulonephritis.

Bell described three cases of acute exudative glomerulonephritis (4, 43). He stated that they were associated with staphylococcal infections, the symptoms of which overshadowed the nephritis. However, within our series, cultures of blood from the biopsy needle in all of our patients were sterile, as were cultures of urine. We have no explanation as to why the kidneys of these patients responded with so much more exudation than proliferation.

That a mixed proliferative and exudative response should occur in post-streptococcal acute glomerulonephritis is not too surprising, but the factors and mechanisms involved are unknown. At present we postulate that most of the lobular scars noted in both the proliferative and exudative groups are monuments of previous focal areas of glomerular exudation or glomerular capillary thrombosis. However, we have little direct evidence to submit on this point because of the relatively few patients with marked glomerular exudation in whom we obtained sufficient serial biopsies. Nevertheless, 8 patients (Table V, group labeled proliferative plus glomerular damage) showed evidence of glomerular proliferation (lobular stalk hypercellularity) along with lobular scars and healed crescents, which could be examples of a mixed response. The disease healed in only three of these patients.

Pathogenesis of chronic glomerulonephritis. Textbooks have taught for many years that acute glomerulonephritis may fail to heal in some patients (4, 12, 34). After clinical subsidence of the acute attack, the only objective sign of disease may be persistent proteinuria, although microscopic hematuria and cylinduria are not infrequent. This phase, often labeled *latent* or *transitional* chronic glomerulonephritis may persist for 10 to 30 years before renal insufficiency, azotemia and finally death in uremia develop (4, 9–11).

The pathogenesis of chronic glomerulonephritis, as defined above, recently has become a subject of controversy. Some workers, Rammelkamp in particular (27), have questioned whether chronic glomerulonephritis is ever the result of an antecedent attack of post-streptococcal acute glomerulonephritis. This viewpoint appears to be based on observations of epidemics of post-streptococcal (Type 12) acute glomerulonephritis in military recruits and school populations (28, 45). As evidenced by disappearance of proteinuria and microscopic hematuria, the renal lesion in practically all patients observed under epidemic conditions apparently healed. However, the majority of the diagnoses of acute glomerulonephritis were made on the basis of mild proteinuria and microscopic hematuria appearing during convalescence from Type 12 streptococcal pharyngitis. Very few patients had edema, hypertension or renal functional impairment. We suspect that the majority of such patients would show few or no lesions on renal biopsy (similar to our presumed focal glomerulitis group, Patients Swi, Ros and Shi).

Information obtained from studies of epidemic nephritis is of obvious importance and value but is not necessarily applicable to acute glomerulonephritis as it occurs sporadically in the adult population. Twelve (or possibly 13 if Jam is included) of our 36 patients with sporadic acute glomerulonephritis following proved streptococcal infections have developed clinical evidence of chronic glomerulonephritis; evidence was obtained that the streptococcus involved in 3 of these 12 patients was Type 12. No evidence of prior renal disease was obtained in any of our patients, and latent periods between the onset of infection and acute nephritis in excess of 1 week were the rule. The "latent period" in exacerbations in chronic glomerulonephritis is generally less than 5 days (26). Other authors have reported similar incidences of chronicity following acute glomerulonephritis (10, 11, 35, 44, 52–54), in some instances associated with proved hemolytic streptococcal infections.

Even though prognosis for healing is better in children (8, 44, 49, 52, 55–58) some authors (59) have reported instances of acute glomerulonephritis following streptococcal infections that failed to heal [also Case 4 of Earle, Taggart and Shannon (60), and Case VN of Wertheim and

co-workers (61)]. Other cases in children of acute glomerulonephritis that failed to heal, in which proof of initial association with a streptococcal infection was lacking, have been reported by several authors (8, 12). The reason for the more favorable prognosis in children is not known. Perhaps examination of the urine following an infection is performed more often in children than in adults, and hence more instances of mild disease are discovered in the young. Pediatricians have often commented (52) that even children very ill with acute glomerulonephritis often recover completely. Perhaps children develop a more severe clinical response to lesser degrees of glomerular exudation or proliferation than do adults. Our data for adults with sporadic poststreptococcal acute glomerulonephritis suggest that a direct relationship exists between the severity of the clinical attack (hematuria excluded) and the prognosis for development of chronic disease (23). Mild clinical attacks usually have healed. The incidence of healing after acute glomerulonephritis, however, is obviously influenced by criteria of diagnosis and for healing (57), as well as by age, epidemicity and other unknown factors.

Classic clinical subacute glomerulonephritis (extracapillary glomerulonephritis of the earlier authors) was not observed in our series, although Patient Cal had typical changes which, however, developed acutely rather than subacutely. Two similar cases, kept alive with the artificial kidney for 75 days, have recently been described (63). The use of the term *subacute glomerulonephritis* to describe other circumstances, such as an episode of the nephrotic syndrome occurring in the course of chronic glomerulonephritis, is confusing. Volhard's (64), Bell's (65) and Ellis's (9) descriptions of the patient who develops acute glomerulonephritis, who never clinically recovers, who dies within 3 months to 1 year of onset with hypertension and uremia, and who, at autopsy, has large, scarred kidneys with many obliterated glomeruli, crescents and severe interstitial fibrosis and edema, delineate very adequately a rather well defined, although uncommon, entity. Our data suggest that subacute glomerulonephritis may be a consequence of a severe initial exudative response.

Good and Vernier (21) have suggested that acute hemorrhagic glomerulonephritis and chronic glomerulonephritis may be independent diseases. They speculate that the occasional apparent progression of acute glomerulonephritis to the chronic form may be due to repeated exacerbations of acute disease, each exacerbation producing further cortical destruction. They cite two children who showed this type of progression clinically and upon serial renal biopsy.

It seems unlikely that repeated exacerbations are the usual cause for progression to chronic glomerulonephritis in adults. None of our 13 patients who developed chronic disease in the present study has so far had exacerbations, although we have observed exacerbations in other patients with chronic glomerulonephritis. Earlier studies on the natural history of poststreptococcal glomerulonephritis also support this conclusion. Loeb, Lyttle, Seegal and Jost (62) clearly showed that recovery is usually permanent following healing in acute glomerulonephritis, since none of 10 patients they followed through Group A streptococcal infections developed chronic glomerulonephritis. Seegal and co-workers (26) defined the clinical characteristics of exacerbations in chronic glomerulonephritis. Their measurements of renal function in such patients demonstrated that exacerbations only rarely accelerated the progression of chronic glomerulonephritis.

Ellis (9) proposed that "Those patients who develop chronic glomerulonephritis after an acute attack have had some renal damage as evidenced by persistent albuminuria, whence we presume there is also some permanent vascular damage which leads to renal ischemia; this renal ischemia eventually leads to renal hypertension, and so a vicious circle is introduced, hypertension causing vascular damage leading to further ischemia and augmented hypertension." Evidence against this point of view includes the absence of any acute vascular damage in renal biopsies we obtained during the acute or the early chronic phases of glomerulonephritis. Our observations, as well as those of Murphy and Schulz (10), that hypertension is an uncommon finding during much of the chronic latent phase of glomerulonephritis, are further points against Ellis's viewpoint. If permanent vascular damage and renal ischemia are to be interpreted as the cause of progressive renal dis-

ease, hypertension would be expected to persist from the acute into the chronic latent phase, or at least to develop early in the chronic phase. Finally, the majority of our patients, even with severe histologic evidence of early chronic glomerulonephritis and considerable interstitial fibrosis, had no evidence of vascular disease. The above remarks are not intended to deny that hypertension or renal vascular disease, if present, could accelerate the progression of chronic glomerulonephritis.

The idea that the glomerular changes induced by the acute attack may become slowly progressive best fits our data concerning the development of chronic glomerulonephritis. We postulate that those patients in the chronic latent group who have prominent foci of lobular stalk thickening and hypercellularity slowly will develop more marked lobulation, gradual hyalinization and scarring of the glomeruli. When glomerular scarring becomes sufficiently severe to compromise efferent arteriolar blood flow to the cortex, ischemic necrosis with consequent scarring and loss of tubular mass should develop. These progressive changes would lead eventually to small, contracted kidneys, azotemia, hypertension, and death in uremia.

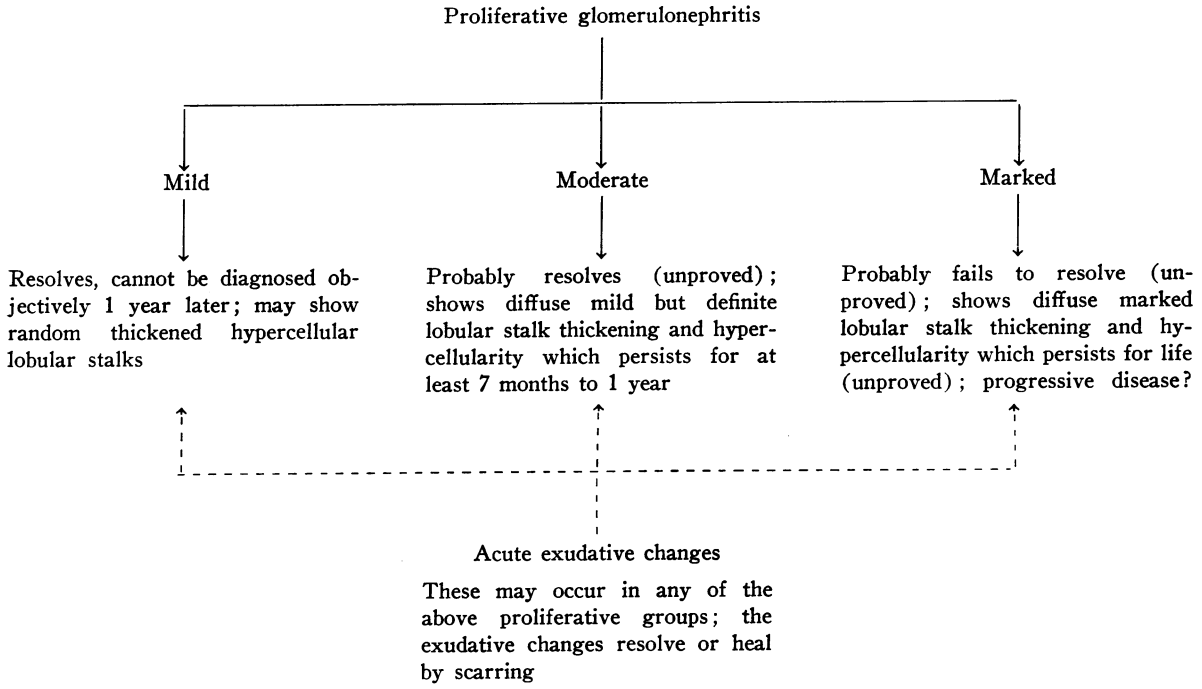
Lobular stalk thickening and hypercellularity were very prominent in 8 of our patients in the latent phase of a chronic glomerulonephritis (Figures 13, 33, 55, 63). These lesions were clearly discerned by Bell in 1936 in his classic paper on chronic glomerulonephritis (65). He named this pathologic lesion *chronic latent glomerulonephritis.* He described it in 8 patients who died of intercurrent diseases while in a clinically silent phase, except for proteinuria, of chronic glomerulonephritis. Bell also noted the similarity of the glomerular lesion of the end-stages of chronic azotemic glomerulonephritis to the lesion of the lobular stalks of the chronic latent phase. He implied that the initial glomerular lesion was progressive and led to the chronic disease.

Both Bell (43) and McGregor (5) noticed the hyaline fibers illustrated in Figure 12. They were present in foci of endothelial cell proliferation during the acute phase. Similar material, clearly shown by electron microscopy to have structural characteristics simliar to the lamina densa of the glomerular capillary basement membrane, is demonstrated in regions of lobular stalk hypercellularity in Patient Mol (Figures 26–28). This material lacks the periodicity of collagen, and, therefore, is not likely to represent scar tissue. Bell (65) implied that these hyaline fibers ultimately lead to the glomerular scarring of chronic glomerulonephritis. This is an attractive hypothesis. However, many of our patients whose disease healed clinically (e.g., Mol, Ser) initially exhibited similar fibrillar material.

Although glomerular damage such as lobular scars, adhesions and crescents usually were associated with the development of chronicity, this was not inevitably the case (e.g., Col, Lee). Apparently these lesions can heal in such a way that clinical cure is possible. Actually, glomerular scarring from the primarily exudative reaction should be a self-limited process. Healing, therefore, might occur late in those patients with a moderately severe acute exudative glomerulonephritis and little endothelial response. A possible clinical counterpart of this phenomenon is suggested by a few patients that Addis (12) reported as having healed several years or more after onset. He aptly labeled this process "healing with a defect."

Diffuse membranous glomerulonephritis (66) was never observed in any of the 36 patients in this series. However, a few patients showed focal basement membrane thickening. For example, some of the peripheral capillary loops of Gar, who had the nephrotic syndrome at the time of biopsy, were thickened due to fibrinoid deposits. Focal thickening of capillary loops also was occasionally observed in areas of thrombosis or necrosis in either focal or diffuse exudative glomerulonephritis. Here the thickening was probably due to deposits of fibrin or other protein on either side of the basement membrane. However, the lack of much significant basement membrane disease together with the frequent finding of thickened basement membranes in idiopathic instances of the nephrotic syndrome is strong evidence that post-streptococcal chronic glomerulonephritis and membranous glomerulonephritis are not only histologically but also etiologically distinct.

The course of the histologic changes in post-streptococcal diffuse proliferative glomerulonephritis is summarized in the following scheme.



SUMMARY

The histopathologic findings and clinical course of 36 patients with post-streptococcal acute glomerulonephritis are reported. All patients were first biopsied within 6 months of onset and have been followed until they healed clinically or developed clinical chronic glomerulonephritis; 56 percutaneous biopsies were obtained.

The 36 patients exhibited much of the spectrum of the renal response to a nephritogenic streptococcal infection. Included are 7 patients whose disease was so mild that the diagnosis rested primarily on laboratory findings and 29 who had overt clinical disease of slight to marked severity. One patient died while anuric 32 days after onset.

Distinctive renal lesions were observed in the glomeruli of 32 patients; 26 showed mild, moderate or marked diffuse proliferative glomerulonephritis, while 6 showed diffuse exudative glomerulonephritis. The glomeruli of the remaining 4 patients showed no distinctive lesions: They have been classified as presumed focal glomerulonephritis; 1 of the 4 had a subacute interstitial inflammatory reaction.

The nephritis had not healed at the last follow-up in 13 patients. In general, these patients had more lobular stalk hypercellularity and evidences of glomerular damage than did those patients who achieved clinical healing.

The relationship of the glomerular lesions observed to the severity of the clinical disease and to the pathogenesis of chronic glomerulonephritis is discussed.

CASE HISTORIES

Case 1. An 18 year old white male (Eva) noted a sore throat and fever which disappeared after several days without treatment of any sort; 10 days later he suddenly developed malaise, anorexia, nausea and pain in one foot. The next day he was admitted to the hospital with pain in both ankles, both knees and both shoulders. His past history was noncontributory except for rheumatic fever 3 years previously. He was treated at that time with steroids for 4 weeks, and was told there was no cardiac involvement.

On admission his temperature was 101.6° F, the blood pressure 130/90 mm Hg, and the joints noted above were tender. Except for a grade 1 systolic murmer at the apex, the remainder of the physical examination was normal. Laboratory tests revealed no anemia, but a moderate leukocytosis and an erythrocyte sedimentation rate (ESR) of 32 minutes in 1 hour (Westergen) were present. The C-reactive protein test (CRP) was positive. On admission, 11 days after onset of the sore throat, the urine had a specific gravity of 1.018, contained no protein, and the centrifuged sediment revealed

only a few leukocytes. A throat culture revealed no hemolytic streptococci, but the serum ASO titer was more than 1,000 Todd U. Over the next 7 months this gradually decreased to 200 U. Serum antibodies were demonstrated against Type 12 streptococci 5 and 6 months after onset, but not against Types 6, 30 or Red Lake. Serum complement was not measured until 5 months after his sore throat. Monthly tests thereafter were all normal. He was placed on bed rest and aspirin, with prompt subsidence of fever and symptoms. Four days after admission, or 15 days after the onset of the sore throat, a routine examination of the urine revealed 2+ protein, numerous erythrocytes and occasional granular casts. At no time was edema, hypertension or gross hematuria noted. The day after admission the BUN was 33 mg per 100 ml; 6 days later this had decreased to 19.5 mg per 100 ml and subsequently was normal. Urine protein increased to 4+. Two months after discovery of abnormal urine, he was excreting 1.8 g per day, and the urinary sediment was still loaded with erythrocytes. At this time the PSP test revealed 50 per cent excretion in 45 minutes, and the urine specific gravity was 1.020 in a concentration test. The proteinuria then gradually improved and disappeared by Day 84 after onset. Some microscopic hematuria persisted until the end of observation, 7 months after onset.

A renal biopsy, obtained 144 days after onset of the renal disease, and 61 days after disappearance of proteinuria, revealed 13 glomeruli, all of which exhibited a moderate degree of lobular stalk hypercellularity (Figure 34). No other glomerular lesions, tubular damage or arteriolar disease was noted. Attempts to discontinue salicylate therapy resulted in recurrences of fever and joint pains until 6 months after onset, when therapy was successfully terminated. He was discharged 7 months after onset, asymptomatic and with normal physical and laboratory findings, except for some erythrocytes in the centrifuged sediment. He has been lost to follow-up.

Case 2. An 18 year old white male (Mol) was treated with aspirin for tonsillitis, with subsidence of symptoms within a few days; 8 days later the urine was examined and found to be normal. However, 22 days after onset of tonsillitis, another urinalysis revealed proteinuria. The next day the tonsillitis recurred. One day later the urine contained 4+ protein, erythrocytes and leukocytes too numerous to count and occasional granular casts; a urine culture was sterile. He was placed on penicillin therapy for 2 weeks. The ASO titer was 625 U, but gradually decreased to 100. At 2 and 6 months after onset serum antibodies against Types 6, 12, 30 or Red Lake streptococci were not present. Serum complement was 30 U (normal: 35 to 50 U) near the onset and ranged between 26 and 34 U during the first 10 weeks after onset. Neither hypertension nor edema developed. The urinary specific gravity in casual specimens ranged between 1.020 and 1.035 throughout the period of observation. PSP excretion in 15 minutes was 35 per cent on admission and 30 per cent 2 months later. The BUN was 24 mg per 100 ml on admission and the urea clearance 48 ml per minute. The BUN decreased to 13 mg per 100 ml within 1 month. The urine became protein-free 2.5 months after onset, while a week earlier an Addis count revealed normal numbers of red blood cells, leukocytes and casts. However, 3.5 months after onset, microscopic hematuria recurred for several days, and one specimen contained 1+ protein. Numerous subsequent urines, however, were normal.

The first renal biopsy (Figure 9) was done 22 days after onset. Proteinuria and marked microscopic hematuria were still present. The BUN had just returned to normal. All the glomeruli were hypercellular, due in part to moderate endothelial cell proliferation, and in part to the presence of as many as 10 eosinophilic and 2 neutrophilic polymorphonuclear leukocytes in the capillary loops of each glomerulus. The capillary loops were decreased in caliber. Many of the proximal tubules contained erythrocytes, while many of the distal tubules contained cellular (polymorphonuclear leukocyte) casts. The cortical architecture was partially disrupted by small foci of immature fibrosis tissue. The arteries and arterioles were normal. A second biopsy was performed 114 days after onset. The urine had been normal for almost 1 month before this biopsy was obtained, but this biopsy was secured during an episode of 1+ proteinuria and microscopic hematuria (44 million erythrocytes in 12 hours) which lasted for approximately 1 week. The biopsy (Figures 23 and 24) showed hypercellular glomeruli. Only an occasional polymorphonuclear leukocyte was seen in the capillary loops. The hypercellularity was focal in nature and confined to the lobular stalk area. The capillary loops were more patent than on the first biopsy. However, adhesions between capillary loops and Bowman's capsule were noted in 3 of the 34 glomeruli present in this biopsy. Occasional small foci of interstitial fibrosis were present.

The urine subsequently examined frequently remained normal. A third biopsy, obtained 205 days after onset and 136 days after disappearance of proteinuria contained 9 glomeruli, 1 of which was hyalinized. Some lobular stalk hypercellularity persisted (Figures 25–28), as did a few foci of mature interstitial fibrosis.

Case 3. A 40 year old white male (Ser) developed gross hematuria 13 days after onset of a sore throat, bronchitis and a temperature of 100° F. Two years previously his blood pressure and urine were normal. Eight days before the gross hematuria he had noted puffy eyes. He visited his physician, who found his blood pressure to be 172/116, with rales at both bases, and with considerable edema of the face and legs. Unfortunately, the urine was not examined, but he was treated with digitoxin and tetracycline hydrochloride. The blood pressure had decreased to 130/94 mm Hg and the edema had disappeared when the gross hematuria developed. The urine remained dark and he was admitted to the hospital 25 days after the beginning of the edema and 17 days after the gross hematuria. On admission the physical examination was normal except for obesity and a blood pressure of 150/96. The ASO titer was 500 U, but after 1 month began to decrease, being 166 U 5 months after onset. On four occasions

between 3 and 21 months after onset, serum antibodies against Type 6, 12, 30 or Red Lake streptococci could not be demonstrated. The serum complement was 20 U on admission, but returned to normal within 1 month. The urine contained 4+ protein, many red blood cells and casts (including blood cell casts). The BUN was 17 mg per 100 ml. The urea clearance was only 18 ml per minute shortly after admission, but within 2 months had increased to 38 ml per minute. PSP excretion was 24 per cent in 15 minutes, and a concentration test revealed a urine specific gravity of 1.020. The hypertension disappeared after 3 days in the hospital. Almost daily urines contained protein during the first 2 months of hospitalization, but thereafter were protein-free. Microscopic hematuria, however, persisted for another 4 months before disappearing.

Four renal biopsies were performed, the first 30 days after onset of edema at a time when proteinuria and hematuria were considerable and the urea clearance was 18 ml per minute. All lobules of all glomeruli were diseased, showing proliferative glomerulonephritis of moderate severity (Figures 3, 4). Numerous polymorphonuclear leukocytes, including eosinophiles, were present in the capillary loops. As many as 15 leukocytes were counted in a single 2 μ section of a glomerulus. Many of the capillary loops were patent but others were obscured by the increased endothelial cells. The tubules contained desquamated brush border material but were otherwise normal and contained no casts. The arterioles were normal and no interstitial reaction was present. The second biopsy (Figures 14–16) was obtained 80 days after onset, 1 week before the proteinuria disappeared. At this time the Addis count revealed 48 million erythrocytes in 12 hours. The urea clearance had increased to 38 ml per minute. Again, all glomeruli were hypercellular, but the hypercellularity was now prominent in the lobular stalks of the glomeruli. As many as 6 polymorphonuclear leukocytes were present in each glomerulus. Several very tiny foci of interstitial fibrosis, not observed in the first biopsy, were present in the cortex, but the cortical architecture was generally intact (Figure 14). The cytoplasm of most of the proximal convoluted tubules contained hyaline droplets. The arteries and arterioles were normal. The third biopsy (Figure 17) was obtained 5 months after onset and more than 2 months after the disappearance of proteinuria. The urea clearance was now 43 ml per minute and a 12 hour urine specimen contained 6 million red blood cells. The histologic findings in this biopsy were very similar to those of the second biopsy, but no glomerular leukocytes or interstitial reaction were present.

After this biopsy the urine remained normal; 26 months after onset a fourth biopsy contained 2 glomeruli, 1 of which was normal while the other revealed only slight lobular stalk hypercellularity (Figure 18).

Case 4. A 24 year old Puerto Rican male (San) noted red urine approximately 6 weeks after a mild sore throat. As far as he knew, he had never had renal disease before. The red urine persisted for 2 or 3 days. Approximately 2 weeks later he complained of cough and right lower chest pain. A physician found a temperature of 103° F and diagnosed pneumonia; the patient was given an injection and some pills. Eight days later he noted puffy eyes, and 2 days after this he was admitted to the hospital. He gave a history of passing worms while living in Puerto Rico and frequent loose stools since the age of 15. On examination he appeared acutely ill. His face and eyes were puffy; his temperature was 101° F, the pulse 74 and the blood pressure 180/102. A generalized lymphadenopathy was noted, but the pharynx appeared normal. A soft blowing systolic murmur was heard at the upper left sternal border. The liver was felt two finger-breadths below the costal margin and was tender. The ASO titer was 250 U on admission, increased to 500 and then gradually decreased to 50 U. Five sera obtained 2 to 24 months after onset contained no antibodies against Type 6, 30, 12 or Red Lake streptococci. The serum complement was very low at first (less than 7 U), but after 1 month began to increase, becoming normal after 5.5 months. Complicating diseases included Manson's schistosomiasis and an active duodenal ulcer. The venous pressure on admission was 220 mm saline. A chest roentgenogram revealed a slightly enlarged heart and pulmonary congestion. On bed rest these findings cleared within 2 weeks, and were associated with a 12-pound weight loss. The urine on admission contained 4+ protein, and by Addis count a 12 hour specimen had 8.4 million red blood cells and 204,000 casts. The proteinuria rapidly decreased so that 6 weeks after onset of gross hematuria, only a trace of protein remained. For the next month, half the urines were protein-free, and thereafter were consistently normal. On admission the BUN was 30 mg per 100 ml, increased within a week to 42, and then returned to normal after another 3 weeks. The PSP excretion near admission was 14 per cent in 15 minutes, but 1 month later had increased to 31 and then 37 per cent. The urea clearance, 1 month after onset, was 63 per cent of normal, and thereafter varied between 75 and 109 per cent of normal. Concentration tests during the first month yielded a maximal urine specific gravity of 1.013.

The first renal biopsy was obtained 32 days after onset of gross hematuria, and at a time when edema, hypertension and a venous pressure of 150 mm saline were still present. The 7 glomeruli in the specimen were very hypercellular (Figures 1, 2, 12). The capillary loops were obscured. Each glomerular lobule was club-shaped, due to the excess number of cells. The glomeruli contained as many as 9 polymorphonuclear leukocytes, and several had 1 or 2 eosinophiles. Considerable protein precipitate was present in Bowman's space of each glomerulus. The cytoplasm of the proximal tubule cells contained hyaline droplets, but no casts were visible. The arteries and arterioles were normal. No interstitial reaction was noted. The second renal biopsy (Figures 21, 22) was performed 73 days after onset, at which time the urine contained only a trace of protein and a few erythrocytes. All 14 glomeruli in the biopsy were diseased, but the hypercellularity was

now focal in nature and confined to the lobular stalks. Some lobular stalks were much more involved than others (Figure 22). In the regions of the hypercellularity, PAS-positive, aniline blue-positive material was present. Most of the glomeruli contained 1 or 2 leukocytes, but one contained 5, including 3 eosinophiles. In contrast to the first biopsy, the glomerular capillary loops were prominent and patent. Some hyaline droplets were still present in the proximal cytoplasm of the tubular cells. The arteries and arterioles were normal, except for a tiny focus of subintimal fibrosis in a branch of a medium-sized artery. A third biopsy, taken 169 days after onset and several months after proteinuria had disappeared, unfortunately consisted mostly of medulla and had but 1 glomerulus. This glomerulus showed focal lobular stalk hypercellularity similar to that observed earlier.

Case 5. A 19 year old white male (Tra) first noted gross hematuria approximately 1 month after an upper respiratory infection. He had no evidence of prior renal disease, and 2 months earlier, blood pressure and urine on admission to the Army were normal. The gross hematuria cleared after several days. The patient did not consult a physician until 18 days later when gross hematuria and malaise recurred. He had no edema and on admission the blood pressure was 124/80. The physical examination was normal. The urine was dark red with a specific gravity of 1.007, and contained 100 mg protein per 100 ml, erythrocytes too numerous to count, many red blood cell casts, and 8 to 10 leukocytes per high-power field. The hemoglobin was 11 g per 100 ml blood and the BUN was 125 mg per 100 ml. Unfortunately, a throat culture was not obtained, but the ASO was 250 U shortly after admission, increased to 500, and then gradually decreased to 125 U. Serum obtained 2, 2.5, and 3.5 months after the first episode of hematuria did not contain antibodies against Type 6, 12, 30 or Red Lake streptococci. Serum complement, first measured 1 month after onset, was slightly decreased (31 to 37 U) but then increased above normal (68 U) and subsequently remained normal (45 U). An oliguria of 200 to 500 ml urine per day was present during the first 2 weeks in the hospital, as were nausea and frequent vomiting. The blood pressure increased to 160/98, but edema never developed. Ten days after admission the patient was critically ill with a BUN of 139 mg per 100 ml, a plasma potassium of 7.5 mEq per L, a pericardial friction rub and a grossly abnormal electrocardiogram. At this time therapy with intravenous adrenocorticotropic hormone (ACTH) was instituted because of the desperate situation. With 2 days a dramatic improvement in all features was noted. Within 2 weeks the BUN had decreased to 60 mg per 100 ml, and was normal (13 mg per 100 ml) by 7 weeks after admission. The urine also rapidly improved, and by the seventh week contained only 1 + protein and a few erythrocytes.

A renal biopsy, obtained in the seventh week (10.5 weeks after the first episode of gross hematuria) contained 15 glomeruli (Figures 63, 64). Both cortex and medulla were present. The architecture of the cortex was distorted by the presence of a rather diffuse interstitial fibrosis. In some areas of dense fibrosis the tubules were atrophic and lined by regenerative-type epithelium. Scattered inflammatory cells, chiefly lymphocytes and macrophages with golden-brown iron-positive pigment in their cytoplasm, were present in some of the areas of fibrosis. This pigment stained negatively for hemoglobin. The glomeruli were all diseased, showing foci of lobular stalk hypercellularity. Several adhesions between capillary loops and Bowman's capsule were present. One large healing crescent was observed (Figure 64); 0 to 1 polymorphonuclear leukocyte was seen in each glomerulus. No vascular disease was observed. Red blood cells, heme casts and hyaline casts were common. After the biopsy, renal function continued to improve so that 5 months after onset PSP excretion had increased to 30 per cent in 15 minutes, and on concentration the urine achieved a specific gravity of 1.030. The urine, however, continued to have 1 + protein and 2 to 3 erythrocytes per high-power field.

A second renal biopsy obtained at this time revealed 11 glomeruli, all of which exhibited thickened lobular stalks with focal hypercellularity. Two glomeruli contained healed crescents and several had adhesions between capillary loops and Bowman's capsule. The cortical architecture was disrupted by multiple small foci of interstitial fibrosis composed of mature collagenous material, some of which contained small collections of inflammatory cells, chiefly lymphocytes. Three months later, or 8 months after onset, the patient had no symptoms, but his urine still contained 1 + protein.

Case 6. A 37 year old white housewife (Ape), whose son had just recovered from tonsillitis, developed a headache, rhinorrhea and a slight sore throat. Her temperature was 102° F. Without treatment the symptoms subsided over several days. One week later, a cough productive of a small amount of sputum developed; 3 days later, or 10 days after the sore throat, she came to the hospital because of this cough. Her two pregnancies, 6 and 1 years previously, had been uneventful—without hypertension, urinary abnormality or toxemia. Two years before she had had a cholecystectomy for calculi and jaundice. Blood pressure and urine were normal at this time. On admission she appeared very obese. Edema was barely demonstrable, but she said that her feet and face felt tight and puffy. Shortly after admission diuresis occurred. She lost 20 pounds in 10 days. Her blood pressure was 170/90. This gradually increased to a maximum of 190/106 2 weeks after admission. A small hemorrhage was noted in the left eyeground. The pulmonic second sound was accentuated and louder than the aortic second sound. This was reversed after several weeks in the hospital. The remainder of the physical examination was within normal limits. A throat culture revealed Group A streptococci, but unfortunately the culture was discarded before the organism could be typed. Roentgenograms of the chest revealed pulmonary congestion and probably bronchopneumonia. She was treated with penicillin for 2 weeks.

The bronchopneumonia and pulmonary congestion gradually cleared. Subsequent throat cultures did not reveal hemolytic streptococci. The ASO titer was greater than 833 U on admission. This gradually decreased to 250 U over the next 2 years. During this time 6 sera failed to reveal antibodies against Type 6, 12, 30 or Red Lake streptococci. The first serum complement was 37 U, but thereafter most values were in the range of 50 to 70 U. On admission the urine contained 4+ protein, many erythrocytes, frequent leukocytes and casts. The BUN was 61 mg per 100 ml. One month after admission the urea clearance was 12 per cent of normal, and the PSP excretion 1 per cent in 15 minutes. The hemoglobin was 10.4 g per 100 ml blood, subsequently decreasing to 7.5. No cause for the anemia, other than azotemia, could be demonstrated. The hemoglobin increased to 13.1 g per 100 ml within 6 months without treatment.

The clinical course and times of renal biopsies in this patient are shown in Chart 2. Three years after onset the blood pressure ranged between 106/65 and 128/90, the urine still contained from 30 to 100 mg protein per 100 ml, occasional erythrocytes and hyaline and granular casts. The urea clearance varied between 79 and 88 per cent of normal. During the follow-up period she had three upper respiratory tract infections and recurrent attacks of sinusitus. None of these was associated with demonstrable hemolytic streptococci. ASO, ASK and AH titers did not increase after any of the infections, nor did exacerbations in chronic glomerulonephritis ensue.

The first renal biopsy, obtained 22 days after onset, contained 13 glomeruli (Figures 40–44). The cortical architecture was disrupted by a generalized edema and immature fibrous tissue. In addition, two small perivascular foci of chronic inflammatory cell infiltration, chiefly lymphocytes and monocytes were present. All glomeruli were diseased. Some glomerular lobulation and a slightly increased number of cells in some lobular stalks were also noted. These areas contained an increased quantity of PAS-positive, aniline blue-positive homogenous material. Numerous polymorphonuclear neutrophiles were present in the capillary loops—as many as 32 per glomerulus. Adhesions between capillary loops and Bowman's capsule and several crescents were present. The arteries and arterioles were normal. Numerous red blood cell and hyaline casts were present in dilated tubules. The second biopsy, obtained 69 days after onset, contained 14 glomeruli (Figures 48–50). The cortical architecture was distorted by foci of mature scar tissue which contained numerous atrophic and regenerating tubules. Edematous connective tissue was present in some areas. All the glomeruli were diseased. They showed lobulation with some slight hypercellularity (Figure 49). In contrast to the first biopsy, almost no inflammatory cells were noted in the glomerular capillary loops. Some healing crescents and adhesions also were present (Figure 50). Hyaline droplets were noted in a few of the epithelial cells over some capillary loops in a few glomeruli. Many red blood

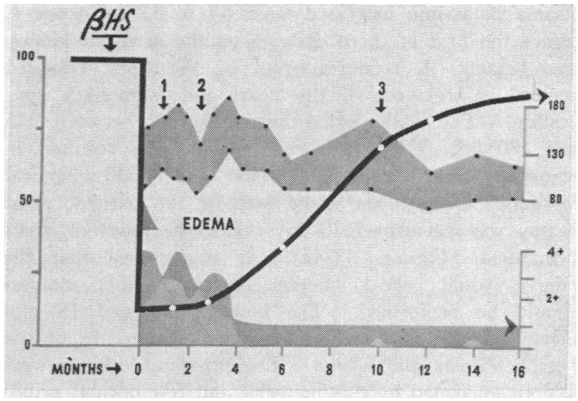


CHART 2. CLINICAL COURSE AND BIOPSIES OF CASE 6. Renal function as per cent of normal is on the left, and the black line represents a plot of estimated renal function at various times after onset. Blood pressure is in mm Hg, proteinuria is on a 0 to 4+ scale, and hematuria is shown by the gray areas on the proteinuria scale. Biopsies were taken at 1, 2 and 3.

cells, heme and hyaline casts were seen in tubules. A few red blood cells were present in Bowman's space of a few glomeruli. One arteriole had a focus of medial and intimal hyalinization. A third biopsy, obtained 307 days after onset, was adequate in size (7 × 1 mm) but was mostly medulla. The medulla was normal except for occasional hyaline casts in the thin loops of Henle. The 1 mm of juxtamedullary cortex present contained an area of scarring with a dense focal lymphocytic infiltration. A single glomerulus was lobulated and scarred. A small tag of nonfibrotic cortex was present.

Case 7. A 34 year old Negro (Cal) was given a single injection of 300,000 U of procaine penicillin by his physician for a moderately severe sore throat. Four days later he noted dark brown urine, which persisted for several days. One week after this he noted decreased urine output and progressive swelling of the feet, abdomen and eyes. During the following week he gained 50 pounds, and finally came to the hospital 3 weeks after the beginning of the sore throat. He knew of no previous renal disease. Physical examination revealed a huge Negro who weighed 355 pounds and was 6 feet, 2 inches tall. His blood pressure was 180/116. Puffy eyes and 2+ pretibial edema were present; the fundi were normal. A grade 3 systolic murmur was heard over the precordium. A throat culture revealed no hemolytic streptococci, but the ASO titer on admission was 333 U and increased to 400 U 10 days later. Serum type-specific antibodies could not be studied, since the patient was on antibiotics throughout his hospital stay. Despite a leukocytosis of 23,000 per mm^3, the serum complement was significantly decreased to 23 U.

The urine contained 4+ protein, many erythrocytes, 10 to 20 leukocytes per high-power field, and frequent granular and fatty casts. The BUN was 134 mg per 100 ml on admission and increased to 177, while the

plasma potassium increased from 6.7 to 8.2 mEq per L before the first of three dialyses on the artificial kidney was begun. A roentgenogram of the chest revealed general enlargement of the heart and pulmonary congestion. The daily urine output varied between 115 and 180 ml. Each of three hemodialyses resulted in transient improvement in clinical and blood chemical findings. Despite the large size of the patient, renal biopsy was performed 30 days after the onset of gross hematuria (Figures 45–47). It was hoped that the biopsy would reveal whether or not further dialyses should be performed. The biopsy contained 16 glomeruli; the cortical architecture was disrupted by diffuse recent fibrosis and edema. The proximal tubules were widely separated by this material and few normal proximal tubules were present; the proximal tubules were lined by rather tall regenerative epithelium. Red blood cell casts were common in the distal tubules. Some widely dilated tubules filled with hyaline casts also were present. The lumens of several proximal tubules were filled with polymorphonuclear neutrophiles, and some of the hyaline casts previously noted contained scattered polymorphonuclear leukocytes and tubular remnants embedded in them. The glomeruli were severely diseased; all showed crescents or some adhesions between peripheral capillary loops and Bowman's capsule; all were hypercellular, primarily because of a marked increase of intracapillary polymorphonuclear neutrophilic leukocytes. As many as 70 to 80 polymorphonuclear neutrophiles and 2 to 3 eosinophiles were present in each glomerulus. The leukocytes appeared to occlude the capillary loops almost completely. The crescents contained several polymorphonuclear leukocytes. Periglomerular fibrous tissue was marked and contained a few polymorphonuclear leukocytes and small collections of chronic inflammatory cells.

Two days after biopsy the patient suffered cardiac standstill, as he was being prepared for dialysis. Cardiac massage restored activity, but the patient died several hours later. An autopsy revealed a flabby heart weighing 500 g and large, swollen kidneys weighing together 810 g. The cortical surfaces were smooth, pale gray-white, and showed no petechial hemorrhages. Microscopically the kidneys showed severe "subacute" glomerulonephritis.

Case 8. A 39 year old white male (Col) noted swelling of feet and eyes, oliguria and dark brown urine 2 weeks after a sore throat. Edema, hypertension, hematuria and proteinuria were noted by his physician, who hospitalized the patient for 11 days. However, shortly after discharge, hypertension increased and he was admitted to the VA Research Hospital. On admission, edema was not present but the blood pressure was 166/118. Aside from a chronic, moderately severe dermatitis of unkown origin that mainly involved the hands and feet, the remainder of the physical examination was normal. The urine contained 1 to 2+ protein and 10 to 25 red blood cells per high-power field but only occasional leukocytes and no casts. The BUN was 22 mg per 100 ml, the PSP excretion was 21 per cent in 15 minutes and on a concentration test the maximal urine specific gravity was 1.018. Throat cultures were not obtained, but the serum ASO titer increased from 166 to 200 U and eventually decreased to 83 U. Type 12 antibodies were demonstrated in the serum 3 months after onset but had disappeared 6 months later. Serum complement remained in the normal range. Hypertension disappeared 2 months after onset as did the nitrogen retention, although the urea clearance was only 51 per cent of normal at this time. Prednisone therapy (40 mg per day) was instituted 5 months after onset, primarily for the skin rash which had flared up and become vesicular. The rash gradually improved during the 2 months of treatment. The urea clearance rapidly returned to normal during the prednisone therapy although proteinuria did not change. Microscopic hematuria had disappeared prior to prednisone therapy. Proteinuria disappeared 26 months after onset. Subsequent urinalyses and 3 Addis counts over the next 18 months were entirely normal.

The first renal biopsy (Figure 51) was obtained 66 days after onset at a time when the urine had 1+ protein and while there was still mild hypertension. One of 12 glomeruli was hyalinized. All the remaining glomeruli exhibited 1 or more lobules with thickened hypercellular lobular stalks, but some lobules were normal and lobular stalk hypercellularity was not a prominent finding; 2 to 3 leukocytes were present in each glomerulus. Three glomeruli had scars, 4 had crescents, and 7 exhibited adhesions. Moderately severe recent as well as old interstitial fibrosis disrupted much of the cortical architecture. Many red blood cell casts were present in the tubules. An arcuate artery exhibited slight subintimal fibrosis. The arterioles were normal. The second biopsy (Figure 52) was obtained 197 days after onset. A trace of protein was still present in the urine, but renal function had returned to normal. This biopsy also contained 12 glomeruli and was very similar to the first, except that the interstitial fibrosis was all old and only a few casts were noted in the tubules. A third biopsy (Figures 56, 57) was obtained 51 months after onset and 18 months after disappearance of proteinuria. This biopsy contained 9 glomeruli, 3 of which were hyalinized. The unhyalinized glomeruli were all slightly diseased, showing in most instances slight lobular stalk thickening and hypercellularity (Figure 57); 2 were almost normal (Figure 56). Crescents were not observed and only two adhesions were noted. Considerably less interstitial fibrosis was present. Only a few hyaline casts were seen in the tubules. No arteries were present, but moderately severe arteriolar changes were seen despite the fact that the patient had been normotensive for almost 50 months and that all arterioles in the two previous biopsies had been normal.

Case 9. A 22 year old white male (Swi) was admitted to a hospital elsewhere, because of a sore throat, fever of 100° to 102° F and a history of a recent weight loss of 10 pounds. On examination the tonsils were red and covered with gray exudate. The right cervical lymph nodes were enlarged. The thyroid was diffusely

enlarged and a fine tremor of the hands was noted. The blood pressure was 140/60; the white blood cell count was 11,200 per mm^3. A throat culture yielded group B hemolytic streptococci. He was treated with penicillin for 10 days. The admission urine contained no protein but did have 5 to 10 red blood cells per high-power field. Twenty-four days after onset of the first tonsillitis attack he again developed a sore throat. The physical examination was as before. The ASO titer was 500 U, subsequently decreasing to 100. Antibodies against Type 12 streptococci, but not against Types 6 and 30, were demonstrated in the serum. The serum complement, first measured 1 month after onset of the urinary abnormalities, was within the normal range for 9 months. The urine contained a trace to 1+ protein, 15 red blood cells per high-power field, and occasional hyaline and granular casts. The BUN was 12.5 mg per 100 ml, the urea clearance 88 ml per minute and the PSP excretion 35 per cent in 15 minutes. The urine continued to contain traces of protein, occasional erythrocytes and casts for 2.5 months. Subsequent urines up to 10 months after onset were normal. A thyroidectomy was performed at this time with no recurrence of the urinary abnormalities.

The first renal biopsy (Figure 67) was obtained 32 days, and the second 79 days, after onset. Traces of protein and occasional red blood cells and casts were present in the urine at the time of both biopsies. The histologic findings in each were similar. The glomeruli were normal. However, several foci of interstitial fibrosis were present, which, in the second biopsy, contained some chronic inflammatory cells. The walls of some arterioles in the largest area of fibrosis were thickened, but elsewhere the vessels were normal.

Case 10. A 20 year old white male (Shi) noted brown urine approximately 1 week after an upper respiratory infection. Shortly thereafter petechiae developed. Four years before, while hospitalized for a brain concussion, he had been told that his urine contained a few erythrocytes. This finding was not investigated further, and, so far as the patient knew, urines examined on admission to the Army 1 year later were normal. On admission to the hospital, his blood pressure was 130/80. The physical examination was normal, except for a moderate number of petechiae. Group A hemolytic streptococci were found on throat culture. The ASO titer, obtained 4 months after the infection, was 166 U. Type 6, 12, 30 or Red Lake antibodies were not found in the serum at this time. The urine contained 1+ protein, many erythrocytes and a few leukocytes. Casts were not seen. The BUN was 17 mg per 100 ml. The urea clearance varied between 95 and 139 per cent of normal. PSP excretion was normal, and after 2 months, casual urine specific gravities as high as 1.030 were recorded. The urine gradually improved and became normal 4 months after onset.

A renal biopsy, obtained 4 months after onset, and 2 days after the urine became normal, contained 17 glomeruli (Figures 65, 66). The cortical architecture was largely intact, although a few scattered tiny periglomerular foci of interstitial fibrosis composed of mature collagenous tissue were noted. These fibrotic foci were free of inflammatory cells but contained atrophic tubules lined with low cuboidal epithelium. One glomerulus was hyalinized; another contained a scarred fibrotic lobule adherent to an area of thickening in Bowman's capsule (healed crescent?) (Figure 66). Several others contained a slight amount of PAS-positive, aniline blue-positive material in some of the lobular stalks, but no focal hypercellularity (Figure 65). Sections of a large muscular artery and numerous arterioles showed no disease. Only a rare cast in some tubules, in the tiny areas of interstitial fibrosis previously mentioned, was present.

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ABBREVIATIONS FOR ALL FIGURES

BUN = blood urea nitrogen in mg per 100 ml; PSP = per cent urinary excretion of phenolsulphonphthalein in 15 minutes after the intravenous injection of 6 mg of dye. Hematuria: numbers indicate the number of erythrocytes per high-power field in a centrifuged fresh urine specimen. H & E = hematoxylin and eosin stain; PAS = periodic acid-Schiff reaction with hematoxylin counterstain; CT = Heidenhain's connective tissue stain.

FIG. 1. SAN, FIRST BIOPSY. This glomerulus is from a 24 year old man who developed clinical acute glomerulonephritis 33 days before biopsy. At the time of biopsy he had 1+ proteinuria, microscopic hematuria; BUN was 34 and blood pressure 156/90. Note the marked hypercellularity. Only a few capillary loops are widely patent. Most are obliterated by endothelial cells with the large vesicular nuclei characteristic of the early stages of acute proliferative glomerulonephritis. An endothelial cell in mitosis is indicated by the arrow. Nine polymorphonuclear leukocytes were present in an average glomerulus from this patient but are not well illustrated at this magnification. The basement membranes are clearly delineated around the edges of the glomerular lobules and are not thickened. The epithelial cells are also normal, as is Bowman's capsule (2μ, PAS, 510×).

FIG. 2. SAN, FIRST BIOPSY. A high-power view of another mitotic figure in the glomerulus shown in Figure 1. This mitosis was in another section about 4 μ deeper in the block. Note the clear attachment of the mitotic cell to the basement membrane. Bowman's capsule is at the top of the figure. A patent capillary is present beneath the capsule. The remaining capillary loops are filled with endothelial cells, the cytoplasm of which contains poorly resolved fibrillar material which is Schiff-positive. These are the hyaline fibers described by earlier authors and do not seem to be the result of fraying of the basement membrane; they are better illustrated in a color photograph of another glomerulus from this patient shown in Figure 12. (2μ, PAS, 1,940×).

FIG. 3. SER, FIRST BIOPSY. A representative glomerulus from a 40 year old man with moderately severe histologic acute proliferative glomerulonephritis. The biopsy was obtained 30 days after onset of the clinical disease, at a time when his urine contained 2+ protein and many erythrocytes; BUN was 17 and blood pressure 136/80. Note that many more capillary loops are patent than in San (Figures 1, 2, 12) but that some lobules are filled with endothelial cells with large vesicular nuclei. Some capillary loops also contain polymorphonuclear neutrophiles. Some variation in the degree of cellularity from lobule to lobule in the glomerulus is noted. The lobule at the arrow is most severely involved, showing a marked increase in the number of endothelial cells. This lobule is illustrated at higher power in Figure 4 (2μ, PAS, 430×).

FIG. 4. SER, FIRST BIOPSY. A high-power view of a part of the lobule at the arrow in Figure 3. Note the large vesicular nuclei of the endothelial cells (1,430×).

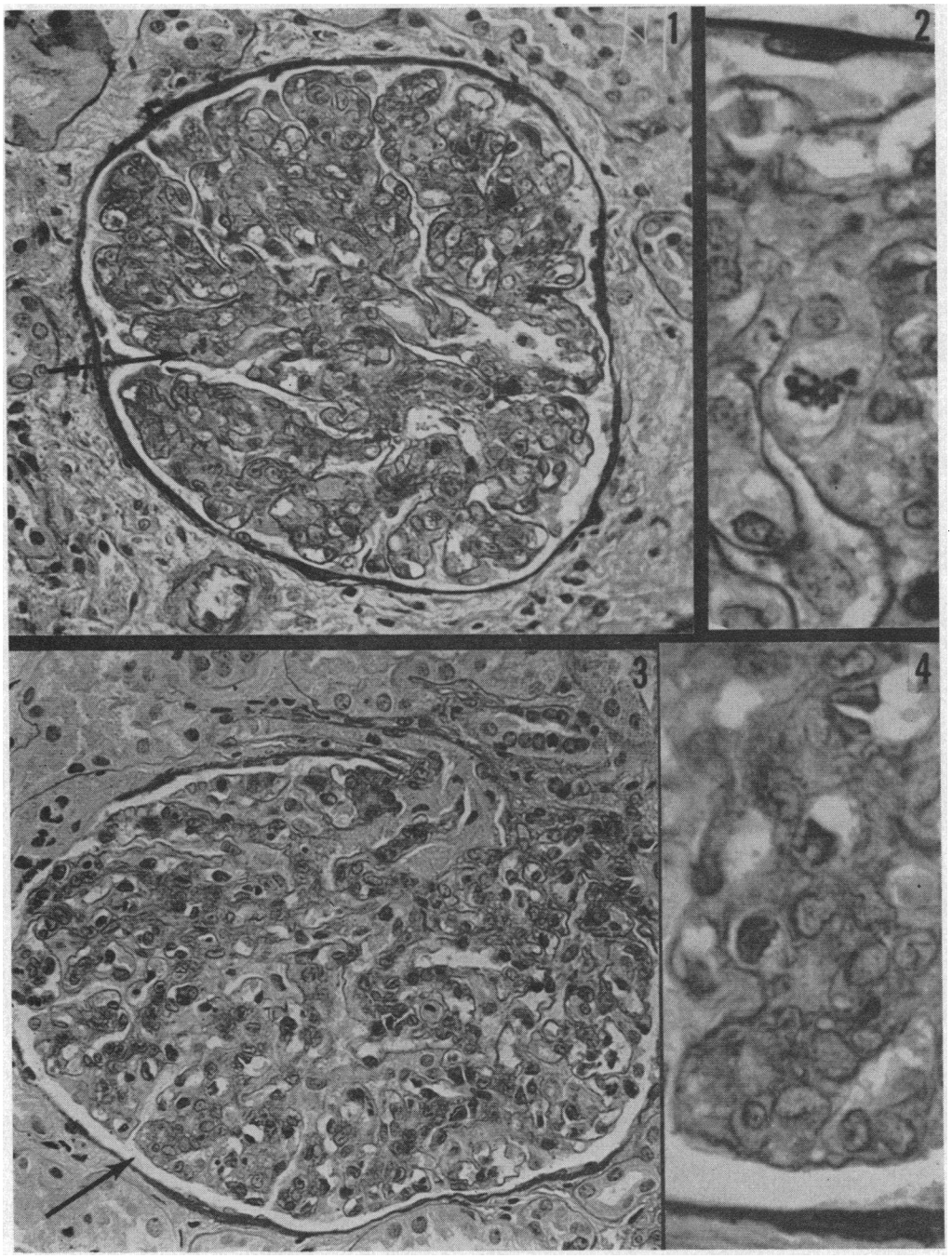
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FIG. 5. BYR, FIRST BIOPSY. A low-power view of the first biopsy from a 17 year old man who had developed clinical acute glomerulonephritis 14 days previously. His urine contained 2+ protein and 20 to 40 erythrocytes; BUN was 17 and blood pressure 124/80 at time of biopsy. The cortical architecture is intact; 4 glomeruli and part of another are visible. All are hypercellular, but the two closest to the center show marked hypercellularity in contrast to the others which are only moderately so. Similar variations in degree of cellularity were common in other patients with acute proliferative glomerulonephritis in this series (2μ, H & E, 214×).

FIG. 6. BYR, FIRST BIOPSY. This glomerulus is from the biopsy of Figure 5; PAS-methenamine silver stain was used in order to accentuate the basement membranes, which stain black with this procedure. This glomerulus illustrates the variation in the degree of cellularity between different parts of the same glomerulus that occurs in acute diffuse proliferative glomerulonephritis. The lobules indicated by the arrows are almost filled with endothelial cells, while the other lobules show much less marked involvement. The cytoplasm of the epithelial cells over the lobule at the lower left contains hyaline droplets. The afferent and efferent arterioles are normal (2μ, PAS-methenamine with hematoxylin counterstain, 450×).

FIG. 7. BYR, FIRST BIOPSY. A high-power view of the lobule at the left-hand arrow in Figure 6, photographed in an adjacent serial section. Endothelial cells fill the capillary loops. Silver-positive fibrils are scattered among the cells. These hyaline fibers have the same staining characteristics as basement membrane (2μ, PAS-methenamine with hematoxylin counterstain, 900×).

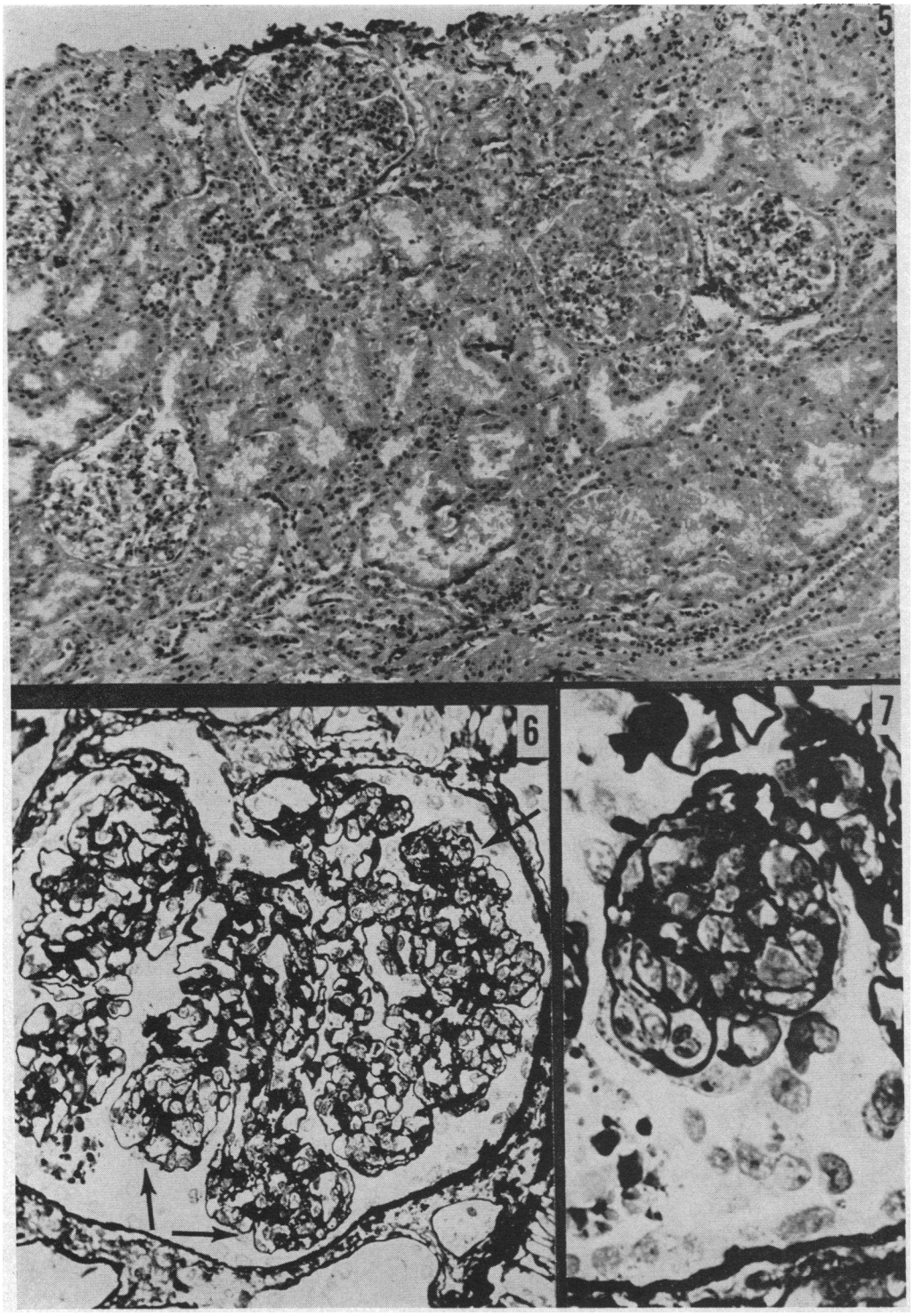
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FIG. 8. BYR, FIRST BIOPSY. Another glomerulus from the biopsy of Figure 5. It contains a crescent, presumably of recent origin (14 days or less). An adjacent section of the crescent showed a mitotic figure. An endothelial cell in mitosis is present at the lower right center. The cell is an anaphase and is illustrated in the insert at a magnification of 2,000× (2μ, PAS, H & E, 800×).

FIG. 9. MOL, FIRST BIOPSY. A representative glomerulus from a 20 year old man; biopsy obtained 22 days after onset of clinical acute glomerulonephritis. At time of biopsy this patient had 2+ protein and many erythrocytes in his urine; BUN was 19, blood pressure 135/62. All glomeruli are hypercellular but some lobules, such as the one at 2 o'clock, are much more involved than others. Note the mitotic figure in tubule cell in the lower left corner. The interstitial tissue is slightly edematous (2μ, H & E, 438×).

FIG. 10. EIK. A representative glomerulus from a 48 year old white male who was biopsied 24 days after onset of clinical acute glomerulonephritis. At biopsy he had 1+ protein and occasional erythrocytes in the urine; BUN was 19, blood pressure 126/90. The glomerulus is mildly hypercellular. An increased number of endothelial cells with rather large vesicular nuclei are noted, particularly near the central portions of the lobules. Most of the capillary loops are rather widely patent. Some contain polymorphonuclear neutrophiles; about 4 were present in this section (2μ, H & E, 328×).

FIG. 11. McC. Many glomeruli in the biopsy obtained 20 days after onset from this 59 year old white man were hyalinized due to arteriolar nephrosclerosis. He had clinical evidence of rather widespread arteriosclerosis. At time of biopsy his urine showed a trace of protein and rare erythrocytes; BUN was 17 and blood pressure 180/90. A representative unhyalinized glomerulus shows a typical, mild, acute proliferative glomerulonephritis. Note the similarity of this glomerulus to that in Figure 10. Many capillary loops are patent. Increased numbers of cells with rather large vesicular nuclei are present near the central portions of many glomerular lobules. Polymorphonuclear neutrophiles are visible in some capillary loops. The granular material in Bowman's space on the lower left is not so-called protein precipitate but is proximal tubular cytoplasm and brush border material that has been compressed in Bowman's space during the trauma of biopsy (2μ, H & E, 450×).

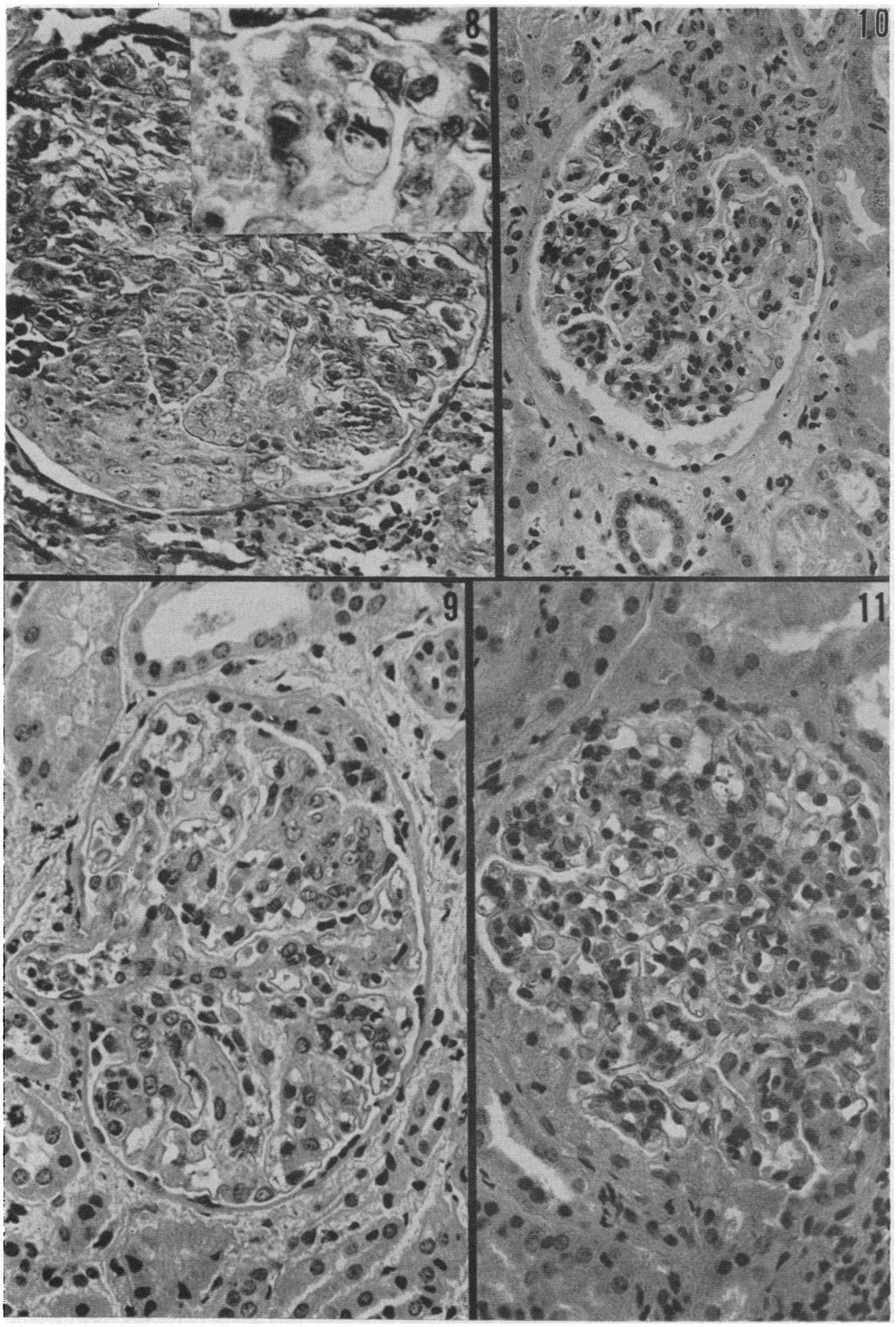
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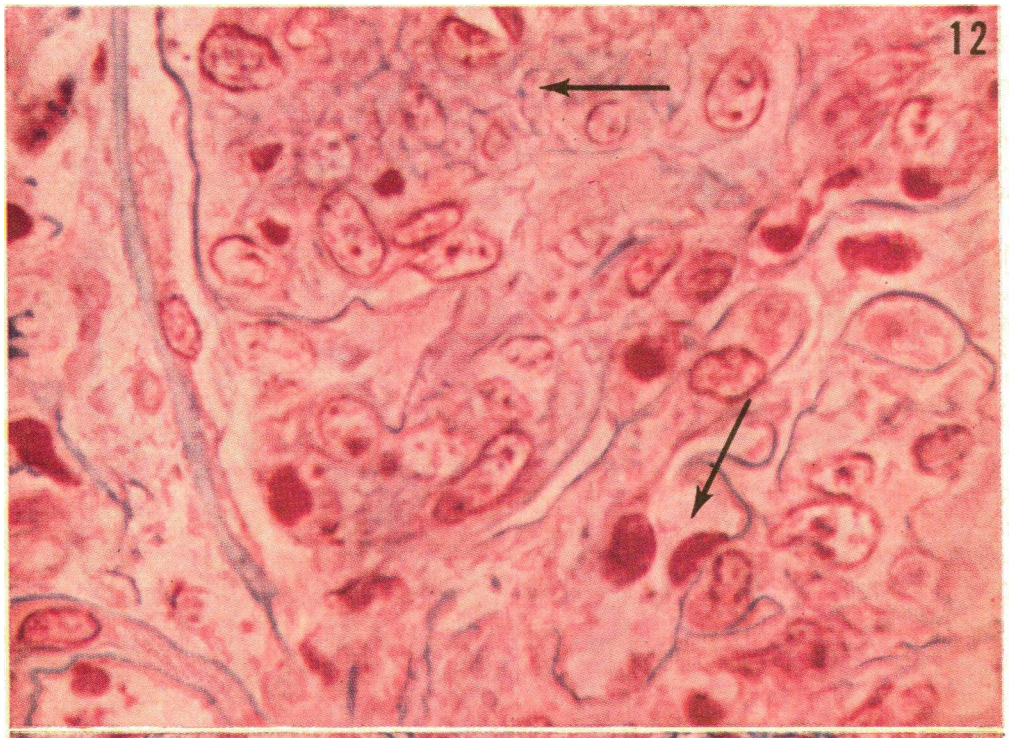
FIG. 12. SAN, FIRST BIOPSY. A high-power view of portions of 3 lobules of a glomerulus from the same patient shown in Figures 1 and 2. Note that the lobules are filled with endothelial cells that are attached to the basement membranes and have rather large vesicular red nuclei. The cytoplasm of these cells contains fine blue hyaline fibers which are well illustrated at the upper arrow. Dense compact chromatin typical of normal glomerular endothelial cells is illustrated by the two nuclei in the capillary at the lower arrow. Reference to Figures 1 and 2 shows that few normal nuclei were present in the glomeruli of this patient. A portion of the normal afferent arteriole to this glomerulus is present in the lower left-hand corner (2μ, CT, 1,000 $\times$).

FIG. 13. LAR. This glomerulus is from a 19 year old male who developed clinical acute glomerulonephritis 79 days before biopsy. At the time of biopsy his urine contained no protein but did have occasional erythrocytes; BUN was 11, blood pressure 145/90. This glomerulus is representative and shows a striking increase in the number of nuclei within the lobular stalks along with aniline blue-positive material, which on close examination has a fibrillar pattern particularly in the lobule at 11 o'clock. Note that the basement membranes and epithelial cells are normal as is the cortical architecture (2μ, CT, 847 $\times$).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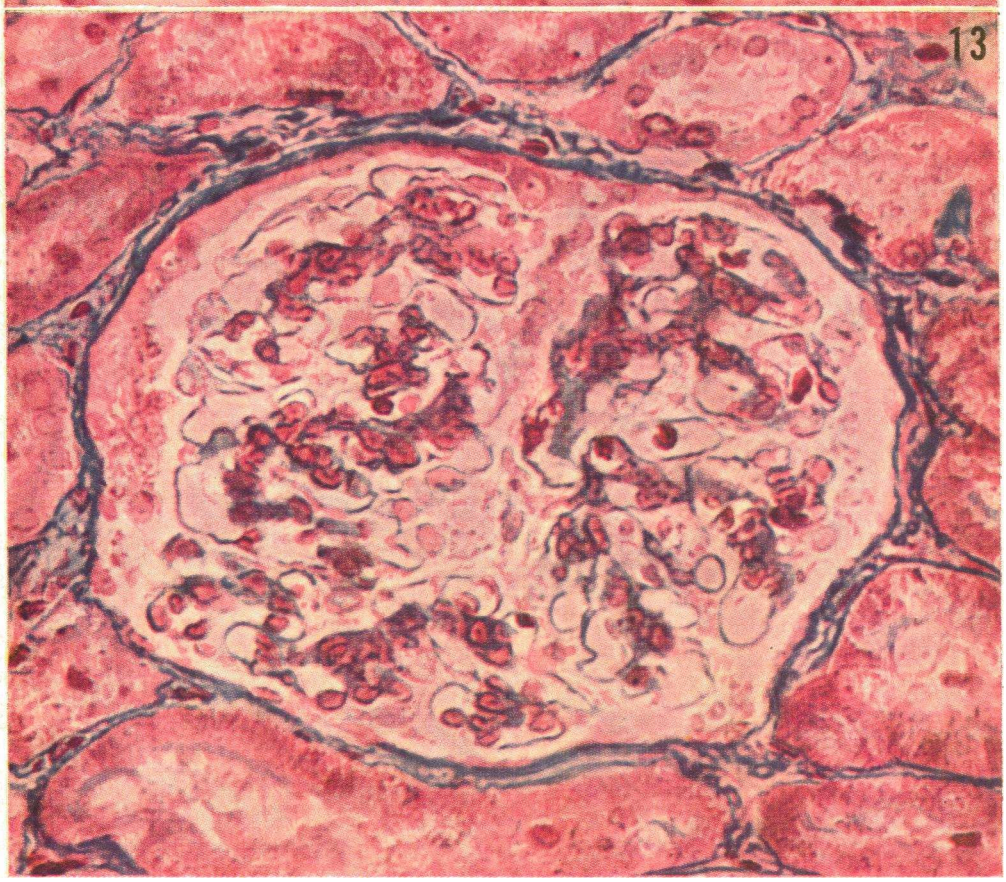
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FIG. 14. SER, SECOND BIOPSY. From the same patient shown in Figures 3 and 4, obtained 80 days after onset of disease. At this time his urine contained a trace of protein and occasional erythrocytes; BUN was 20, blood pressure 124/80. This low-power view of the middle two-thirds of the biopsy shows the cortical architecture to be intact. Each glomerulus is diseased and shows thickened lobular stalks. The glomerular changes are illustrated in detail in Figures 15 and 16 (2μ, PAS, 65 $\times$).

FIG. 15. SER, SECOND BIOPSY. A higher-power view of a glomerulus from the biopsy of Figure 14. Note the increased number of nuclei and PAS-positive material in each lobular stalk. The degree of involvement varies from lobule to lobule. Those at 3, 4, and 6 o'clock are thicker and contain more cells than the others. The basement membranes are of normal thickness and most of the capillary loops are widely patent. Compare the appearance of this glomerulus with that of the glomerulus from the first biopsy of this patient, shown in Figure 3. The hypercellularity is much more diffuse in the earlier biopsy, and the glomeruli contain more inflammatory cells and fewer patent capillary loops than do those in the second biopsy (2μ, PAS, 556 $\times$).

FIG. 16. SER, SECOND BIOPSY. Another glomerulus from the biopsy of Figure 14 to illustrate that some glomeruli in the subsiding stages of a proliferative glomerulonephritis may have much less involvement than others. The lobular stalks at the arrows are slightly thickened and hypercellular but are less diseased than the lobules of the glomerulus shown in Figure 15 (2μ, PAS-methenamine with hematoxylin counterstain, 450 $\times$).

FIG. 17. SER, THIRD BIOPSY. Obtained 76 days after the second biopsy shown in Figure 14, and 156 days after onset of the clinical disease. At the time of third biopsy the urine had been protein-free for 66 days; BUN was 13, blood pressure 138/80. Note that the lobular stalks are still hypercellular and that the general appearance of this glomerulus is similar to that of glomeruli in the second biopsy. The nuclei of the lobular stalk cells appear smaller and less vesicular than during the acute phase. Many of the nuclei also now contain prominent nucleoli. The basement membranes and the arteriole at the hilus are normal (2μ, H & E, 500 $\times$).

FIG. 18. SER, FOURTH BIOPSY. A micrograph of one of the two glomeruli obtained 775 days after onset of clinical disease and 685 days after the urine became protein-free. The lobular stalks at the arrows are slightly thicker and more cellular than normal. The other lobules are normal, as is the arteriole. The other glomerulus from this biopsy was normal (2μ, CT, 660 $\times$).

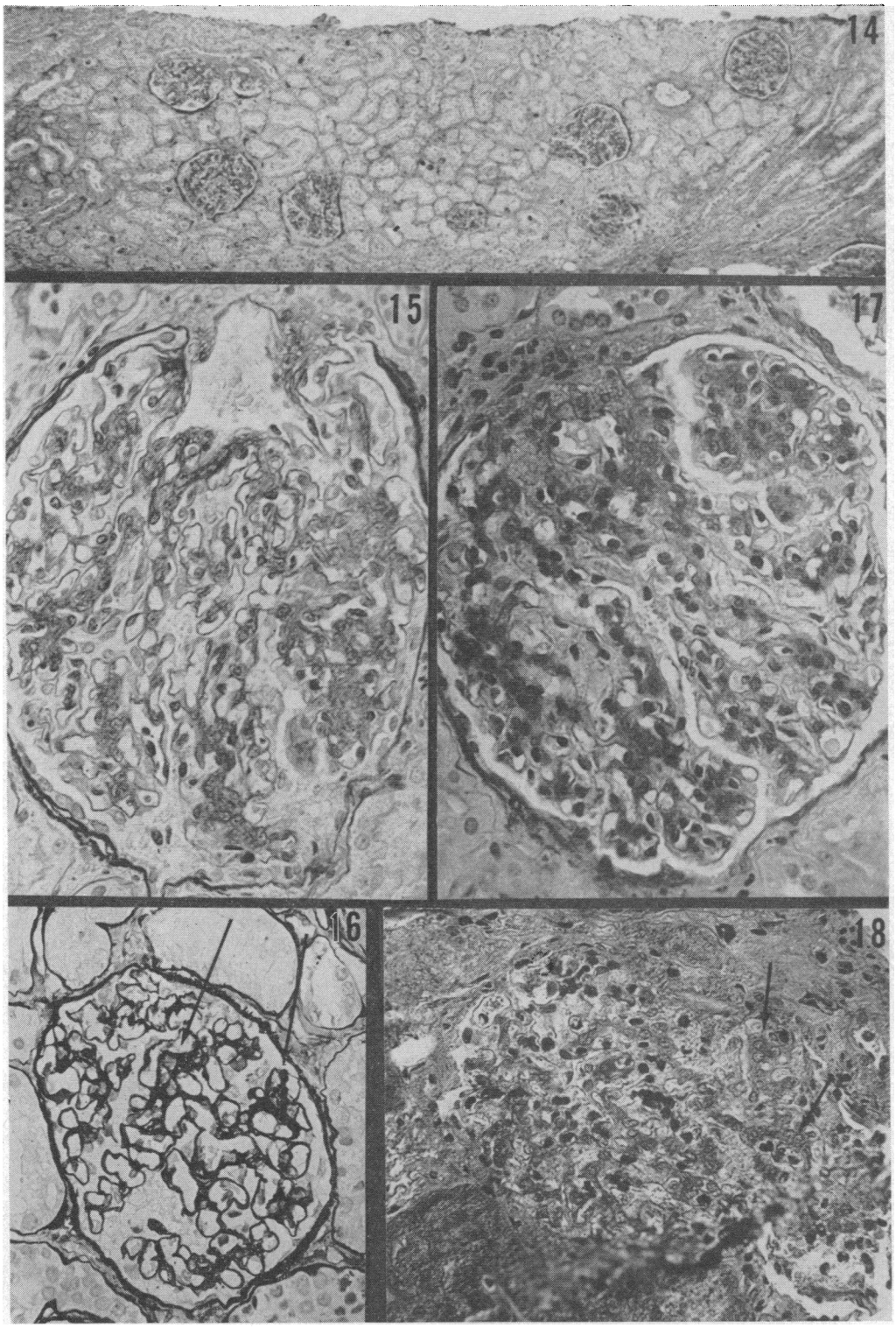
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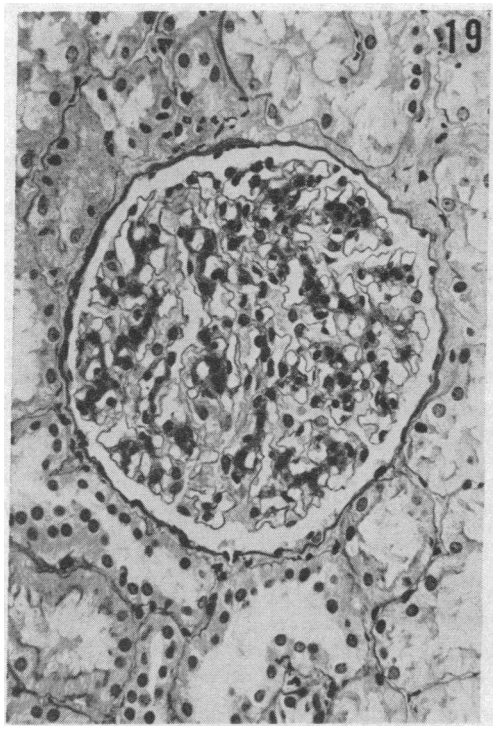
FIG. 19. BYR, SECOND BIOPSY. Obtained 115 days after onset and 101 days after the first biopsy of Figures 5–8. At the time of second biopsy his urine had 2+ protein and 20 to 30 erythrocytes; BUN was 14, blood pressure 120/80. This is a representative glomerulus which shows small foci of lobular stalk hypercellularity. The basement membranes and tubules are normal (2μ, H & E, 356×).

FIG. 20. BYR, SECOND BIOPSY. This is another glomerulus from the biopsy of Figure 19. It illustrates abundant silver-positive material in the lobular stalks. The endothelial nuclei in this area are obscured by the silver desposits (2μ, PAS-methenamine, 356×).

FIG. 21. SAN, SECOND BIOPSY. Obtained 73 days after onset and 40 days after the first biopsy, which is shown in Figures 1, 2 and 12. At the time of second biopsy the patient's urine showed a trace of protein and occasional red blood cells; BUN was 12, blood pressure 110/52. This is a representative glomerulus and exhibits hypercellular and thickened lobular stalks similar to those in Figures 15, 17 and 19 from other patients with subsiding acute proliferative glomerulonephritis. The lobules at 1 and 3 o'clock show slightly more severe disease than the other lobules in the glomerulus (2μ, H & E, 512×).

FIG. 22. SAN, SECOND BIOPSY. This high-power view illustrates a focus of marked lobular stalk involvement from the same biopsy of Figure 21. Note that basement membranes are normal around the periphery of the loops. The nuclei in the center of the stalk are located in cytoplasm and no discrete cell membranes are present. The cytoplasm contains poorly resolved hyaline fibers that are blue with this stain and are similar to those noted in Figure 13. (2μ, CT, 1,960×).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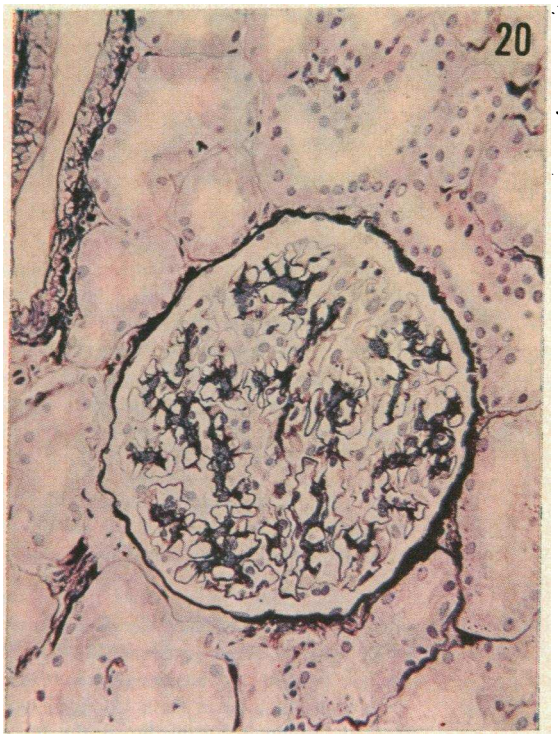
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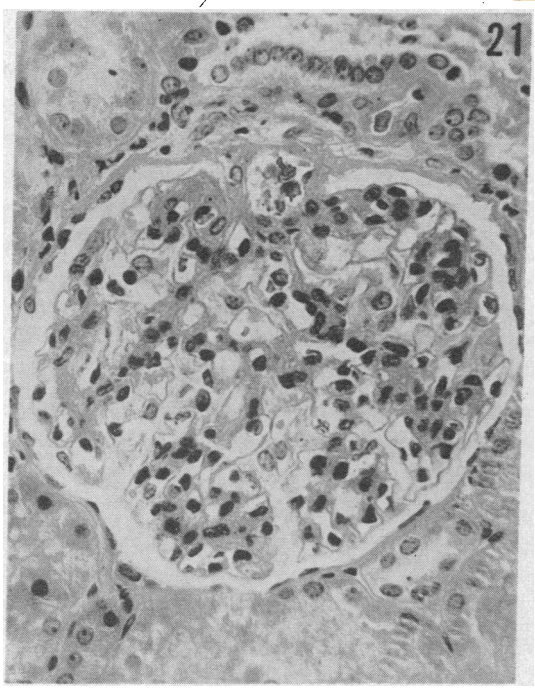
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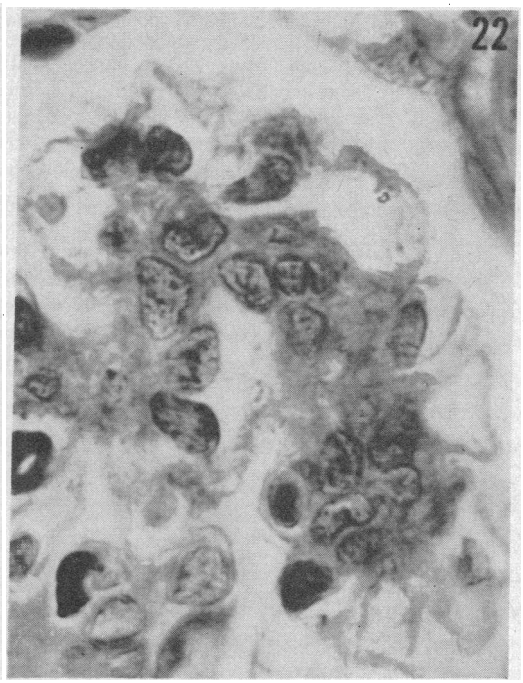
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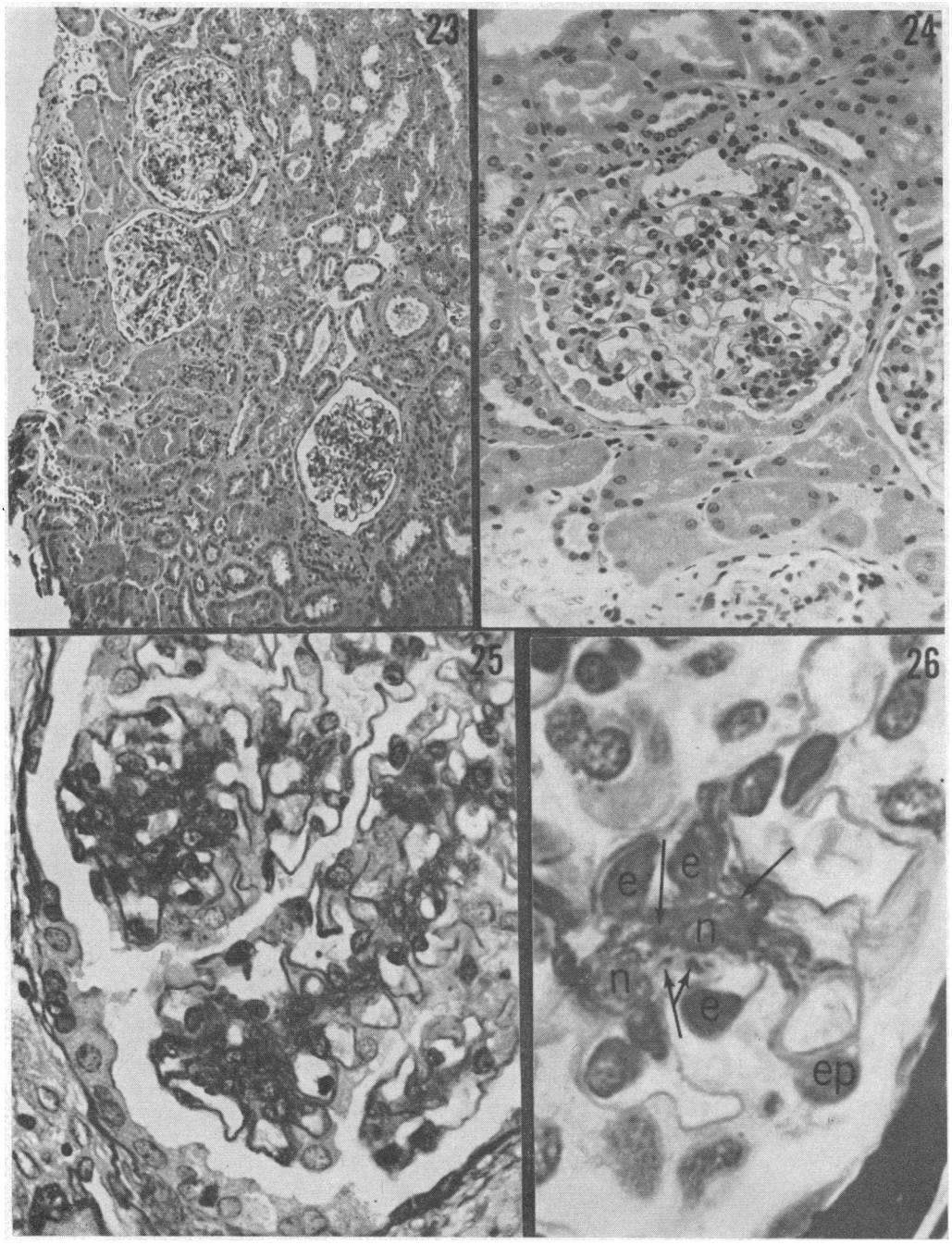
FIG. 23. MOL, SECOND BIOPSY. Obtained 114 days after onset and 92 days after the first biopsy (Figure 9). At the time of second biopsy this patient had 1 + proteinuria and many red blood cells in his urine; blood pressure was 120/60. This low-power view shows 3 glomeruli sectioned near the midplane. The interstitium is normal. Red cell casts are present in collecting ducts near the center of the photograph. The glomeruli show lobular stalk hypercellularity of moderate severity. The glomerulus at upper left is illustrated in Figure 24 (2μ, H & E, 193 $\times$).

FIG. 24. MOL, SECOND BIOPSY. A high-power view of the glomerulus at the upper left in Figure 23; it clearly shows 3 foci of rather marked lobular stalk thickening and hypercellularity at 1, 2 and 5 o'clock (2μ, H & E, 328 $\times$).

FIG. 25. MOL, THIRD BIOPSY. Obtained 205 days after onset and 183 days after the first biopsy. At the time of this biopsy the patient's urine was normal; BUN was 8, blood pressure 125/60. This glomerulus shows some crushing artifact in that the basement membranes of the capillary loops are irregular. Note that the lobular stalk lesion is very similar to that present in the second biopsy. Bowman's capsule on the lower left is lined by cuboidal epithelium, a finding occasionally noted in normal kidneys (2μ, PAS, 850 $\times$).

FIG. 26. MOL, THIRD BIOPSY. Silver-positive hyaline fibers are indicated by the arrows in the middle of a small focus of lobular stalk hypercellularity (same biopsy as Figure 25). These fibers exhibit the staining reactions of glomerular basement membrane. They are positive to the PAS reaction, stain blue with aniline blue, and react with silver after digestion with dilute periodic acid. Collagen also shows these reactions. However, electron micrographs (Figure 27) show that these fibers lack the periodicity of collagen and we assume, therefore, that they are a product of the endothelial cells with a consistency similar to that of the basement membrane of the glomerular capillary loops. The nuclei of the cells of the lobular stalk are at n, the nuclei of the endothelial cells attached to the basement membrane are at e, and an epithelial cell is at ep (2μ, PAS-methenamine with hematoxylin counterstain, 1,850 $\times$).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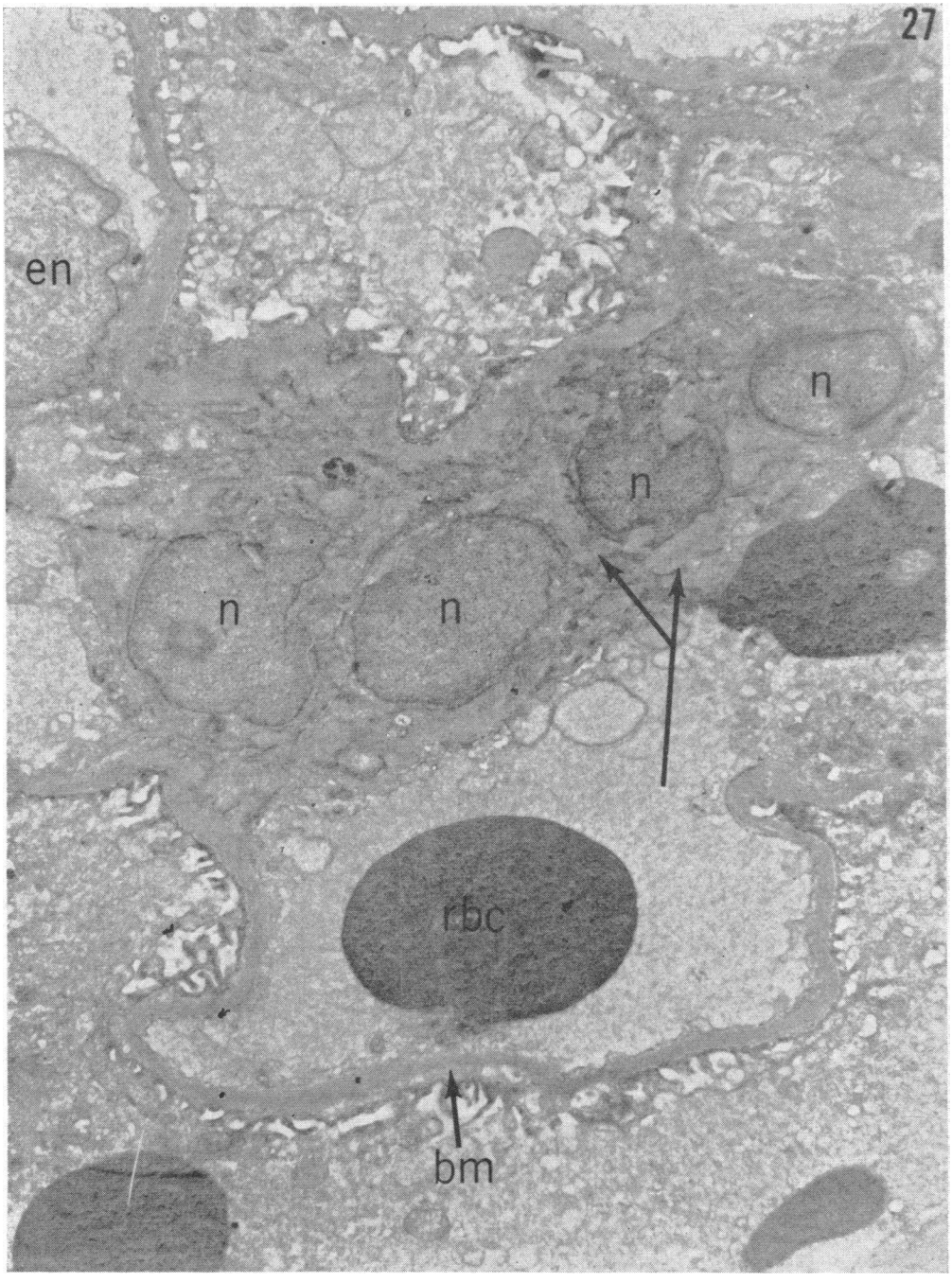
e
e
n
n
e
ep

FIG. 27. MOL, THIRD BIOPSY. Electron micrograph of a portion of a glomerulus to show one focus of lobular stalk hypercellularity under higher magnification. The basement membrane of the glomerular capillary is at bm. Normal foot processes of the epithelial cells are clearly visible over the outer surface of the capillary and a thin layer of endothelial cytoplasm is present on the lumen side. Two erythrocytes (rbc) are present inside the capillary. A hypercellular lobular stalk, which is covered by basement membrane and foot processes at the top and a thin layer of vesicular endothelium at the bottom, is present in the center of the figure. It contains 4 nuclei (n). Note that no cell membranes are present between the nuclei and that the cytoplasm of the stalk area contains numerous irregular hyaline fibers, some of which are identified by arrows. A portion of a normal endothelial cell is shown at en. No nuclei of epithelial cells are visible in the photograph (7,600 ×).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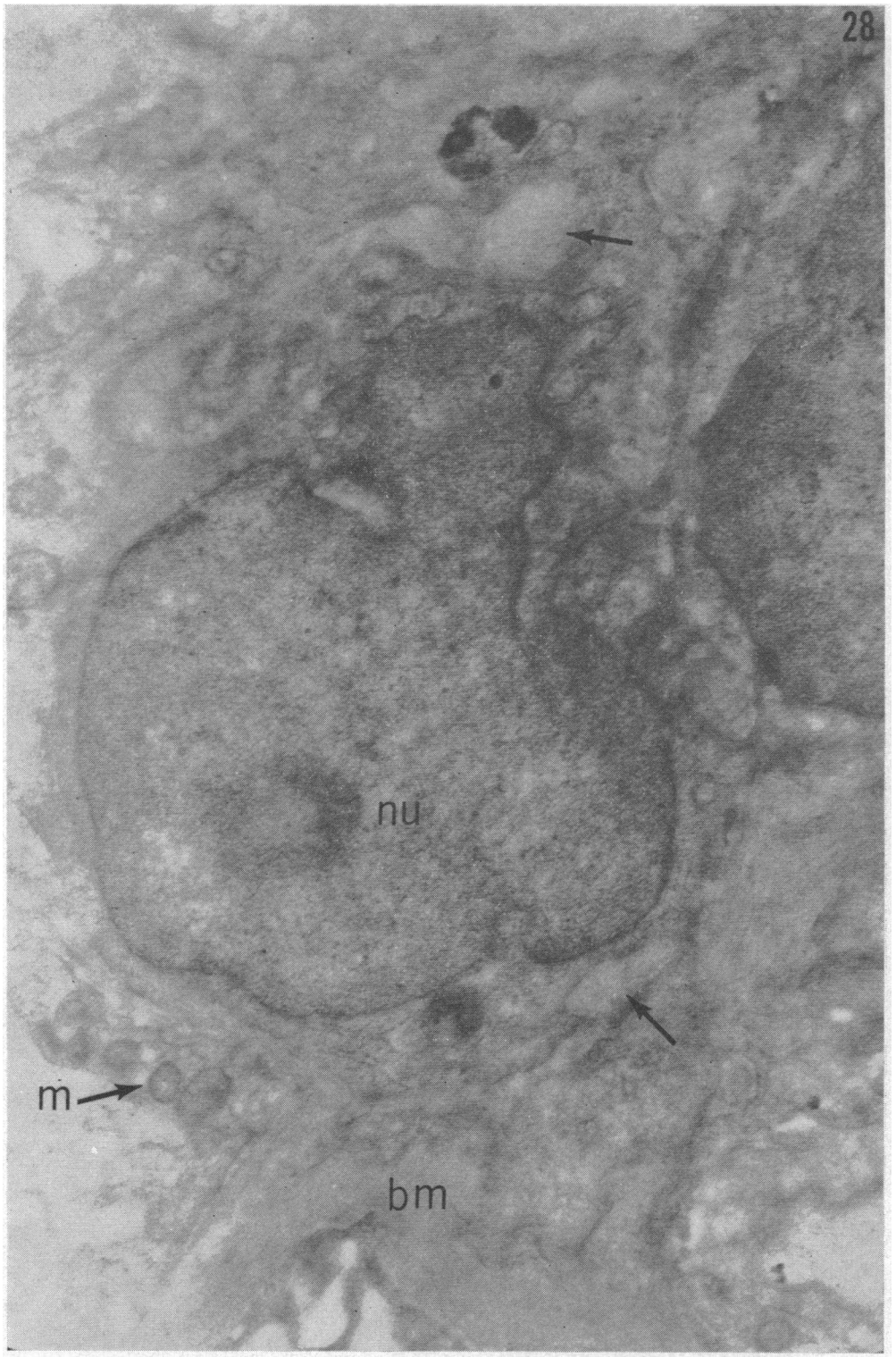
en
n
n
n
n
rbc
bm

FIG. 28. MOL, THIRD BIOPSY. Higher-power view of the lobular stalk cell containing nucleolus (nu) on the left-hand side of Figure 27. Note the 3 mitochondria (m) in the cytoplasm of the endothelial cell and a portion of normal basement (bm). The hyaline fibers at the arrows are surrounded by tubular elements of the endoplasmic reticulum. The density and structure of the fibers are similar to the basement membrane of the capillary loop at bm. Note that the hyaline fibers show none of the fibrillar pattern and periodicity of collagen. The endoplasmic reticulum appears to be connected to the nucleus in some areas, particularly near the small bit of dense osmophilic material at the top of the figure (27,750 ×).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nu
m
bm

FIG. 29. MAR. Obtained from a 57 year old white male 30 days after onset of acute post-streptococcal glomerulonephritis and illustrates a thrombus in a glomerular capillary loop. Note that the basement membrane of the capillary containing the thrombus is thickened but that the others in the section are normal. At the time of biopsy the patient's urine contained 2+ protein and 40 to 50 erythrocytes; BUN was 28, blood pressure 148/80. All lobules contain increased numbers of intracapillary cells with large vesicular nuclei. The lobules at 8 to 9 o'clock contain many more polymorphonuclear neutrophiles than other lobules in the glomerulus. This patient exhibits a mixed proliferative and focal exudative response (2μ, H & E, 470×).

FIG. 30. DIL. This glomerulus is one of the most severely involved of 22 in a biopsy obtained from an 18 year old white male 82 days after onset of a very mild clinical acute glomerulonephritis. At the time of biopsy his urine contained no protein and 10 erythrocytes; BUN was 12, blood pressure 130/80. The glomerulus shows 2 obvious thickened hypercellular lobular stalks but is otherwise normal (2μ, H & E, 484×).

FIG. 31. DIL. Another glomerulus from the patient of Figure 30. It is representative and normal except for 3 slight foci of lobular stalk thickening and hypercellularity near the center and at 1 and 5 o'clock (2μ, PAS, 625×).

FIG. 32. LAT. A low-power view of approximately one-quarter of the biopsy. The tissue was obtained 122 days after onset, at which time the urine contained 1+ protein and 1 to 3 erythrocytes; BUN was 25, blood pressure 135/95. The cortical architecture is intact. All glomeruli in the biopsy are diseased, showing lobular stalk thickening and hypercellularity (2μ, H & E, 139×).

FIG. 33. LAT. High-power view of a glomerulus from the same patient of Figure 32 to show the characteristic glomerular lesion of subsiding acute proliferative post-streptococcal glomerulonephritis. The extent of the lobular stalk involvement as to degree of thickening, hypercellularity and number of lobules markedly involved is greater than in any of the patients so far illustrated. This patient's nephritis failed to heal (2μ, H & E, 554×).

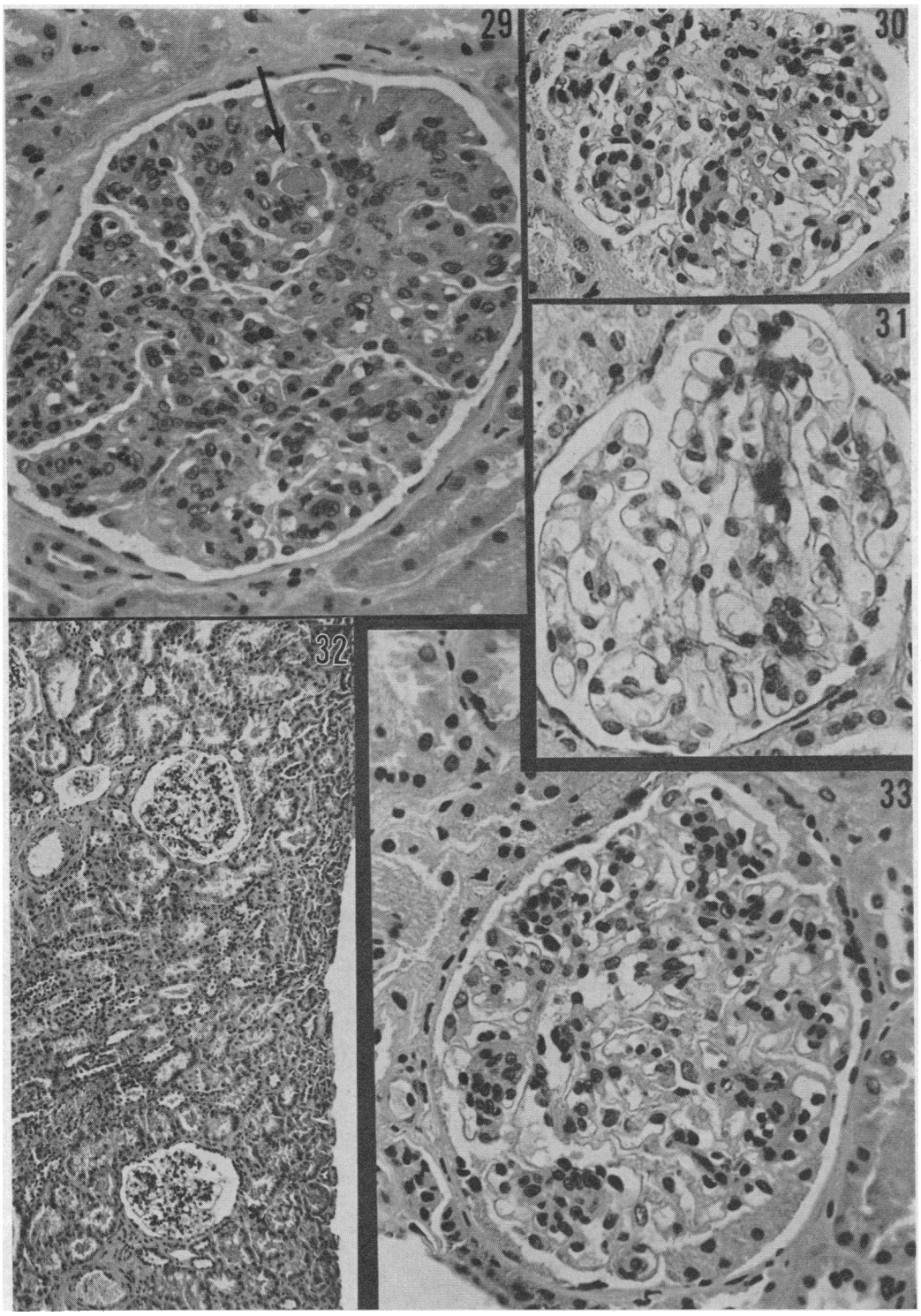
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FIG. 34. EVA. A representative glomerulus from a patient described in detail in the protocols (Case 1). At the time of biopsy his urine showed many erythrocytes but no protein; BUN was 15, blood pressure 130/80. The characteristic lobular stalk hypercellularity of an antecedent acute proliferative glomerulonephritis is clearly demonstrated (2μ, H & E, 676 $\times$).

FIG. 35. BIS. This micrograph is one of the most severely involved glomeruli found in the biopsy of a 21 year old man's kidney 146 days after onset. At the time of biopsy his urine contained 2 + protein and 20 to 50 erythrocytes; BUN was 20, blood pressure 110/80. Note adhesions at 7 and 10 o'clock and the increased intracapillary cells, primarily located in the stalks of the lobules. The black objects are erythrocytes which stain bright scarlet with azocarmine and, with a green filter, photograph deep black (2μ, CT, 495 $\times$).

FIG. 36. SCH. This micrograph includes on the left the most severely involved of the 36 glomeruli obtained from this 18 year old white male 132 days after onset of disease; seven days after this biopsy his urine became protein-free. At the time of biopsy his urine showed a trace of protein and 2 to 4 erythrocytes; BUN was 15, blood pressure 122/66. The right-hand glomerulus is not representative of the glomeruli in the biopsy, since it shows less lobular stalk hypercellularity than most of the other glomeruli. The left-hand glomerulus shows a lobular scar and adhesion (2μ, H & E, 309 $\times$).

FIG. 37. MOE. A low-power view from a biopsy taken from an 18 year old white male 170 days after onset. At the time of biopsy his urine showed a trace of protein and an occasional erythrocyte; BUN was 18, blood pressure 125/80. This representative glomerulus shows the lobular stalk involvement characteristic of the subsiding phase of post-streptococcal proliferative acute glomerulonephritis (6μ, PAS, 326 $\times$).

FIG. 38. ROO, FIRST BIOPSY. A glomerulus from a biopsy taken 47 days after onset in a 59 year old white male. At the time of biopsy his urine showed 1 + protein and rare erythrocytes; BUN was 20, blood pressure 120/70. This glomerulus is representative of mild acute proliferative glomerulonephritis. The endothelial cells which are present in slightly greater than normal numbers have large vesicular nuclei (2μ, H & E, 450 $\times$).

FIG. 39. ROO, SECOND BIOPSY. Obtained 602 days after onset and 249 days after the urine became protein-free. This glomerulus is normal, as were all others in the biopsy (2μ, PAS, 450 $\times$).

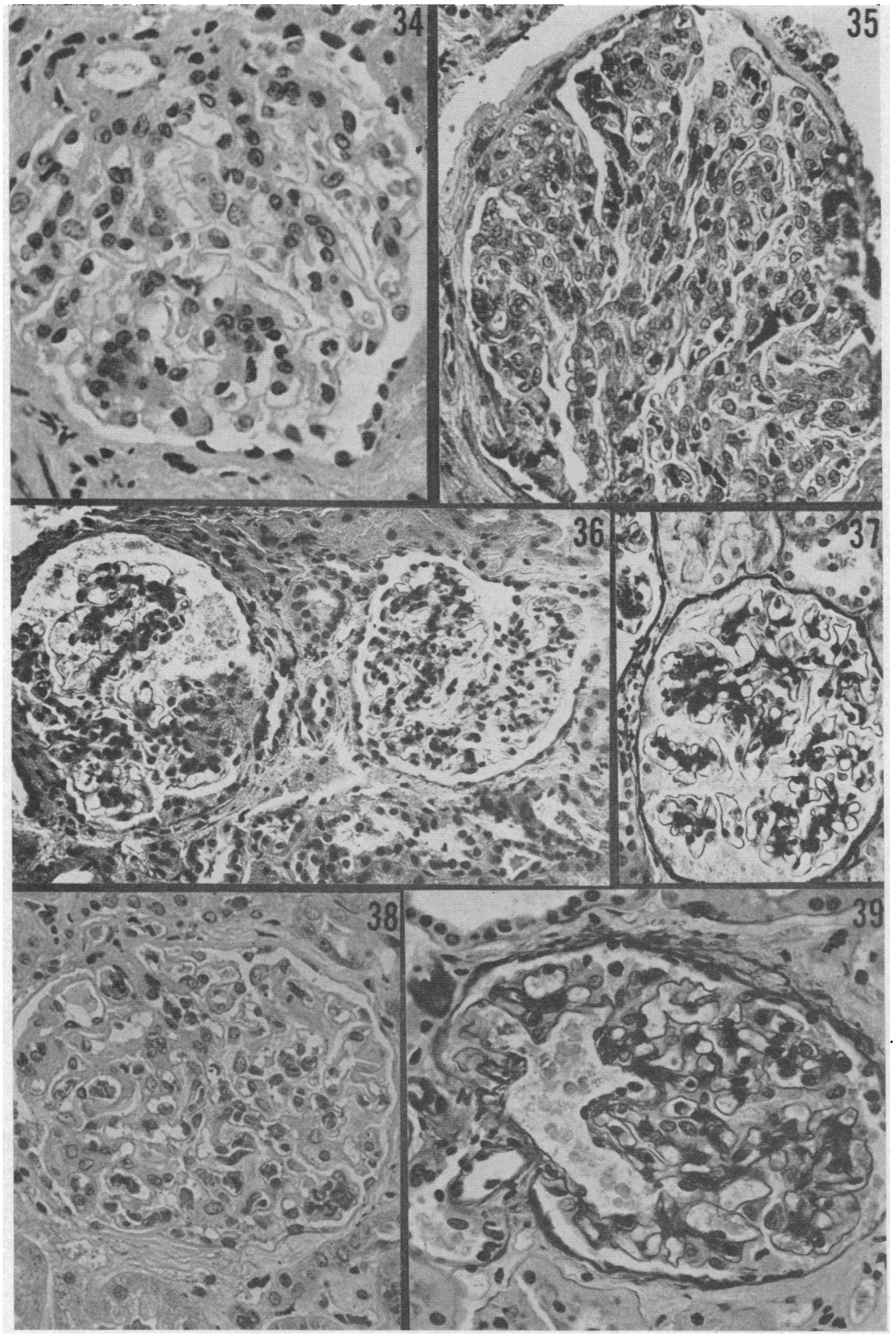
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FIG. 40. APE, FIRST BIOPSY. See Case 6 in the protocols for detailed history. This 39 year old woman had severe clinical acute glomerulonephritis. A low-power view of about one third of the biopsy illustrates the severe cortical edema shown by the entire biopsy; at this time her urine showed 3+ protein and many red cells and red cell casts; BUN was 52, blood pressure 180/100. The black casts in the center of the micrograph are red cell casts in collecting ducts (2μ, CT, 59×).

FIG. 41. APE, FIRST BIOPSY. This hypercellular glomerulus is from the same biopsy shown in Figure 40. About 20 acute inflammatory cells are present in the capillaries and some lobules show a slight increase in the number of endothelial cells. Note the cells with large vesicular nuclei at the arrow (2μ, H & E, 450×).

FIG. 42. APE, FIRST BIOPSY. Another glomerulus from the biopsy of Figure 40. A large crescent is present on the lower half of Bowman's capsule. The capillary loops are adherent to the crescent at 7 o'clock and to Bowman's capsule at 1 o'clock (6μ, CT, 281×).

FIG. 43. APE, FIRST BIOPSY. A necrotic glomerulus from another section of the biopsy of Figure 40. The glomerulus is infiltrated with numerous polymorphonuclear neutrophiles and adherent to Bowman's capsule over one-half of its circumference. The adjacent interstitial tissue is edematous and the tubules which are present are lined by flattened or regenerative epithelium. The tubule at the upper left contains a red cell cast (2μ, H & E, 332×).

FIG. 44. APE, FIRST BIOPSY. A glomerulus from another part of the biopsy of Figure 40. Many of the capillary loops have a diminished diameter because of swelling of their endothelial lining (arrow at center) while others are occluded by polymorphonuclear neutrophiles. The polymorphonuclear cells have completely occluded the lobule at the upper left. This represents severe focal exudation, and is a phenomenon that we believe is often followed by lobular scarring (see Figure 50 for the appearance of the possible end-stage of this lesion). Note that new endothelial cells are not common and that the chief cause of the loss of glomerular filtering surface in this patient is edema and the polymorphonuclear cell infiltration. The basement membranes are normal and no capillary thrombi are present (2μ, PAS-methenamine with hematoxylin counterstain, 850×).

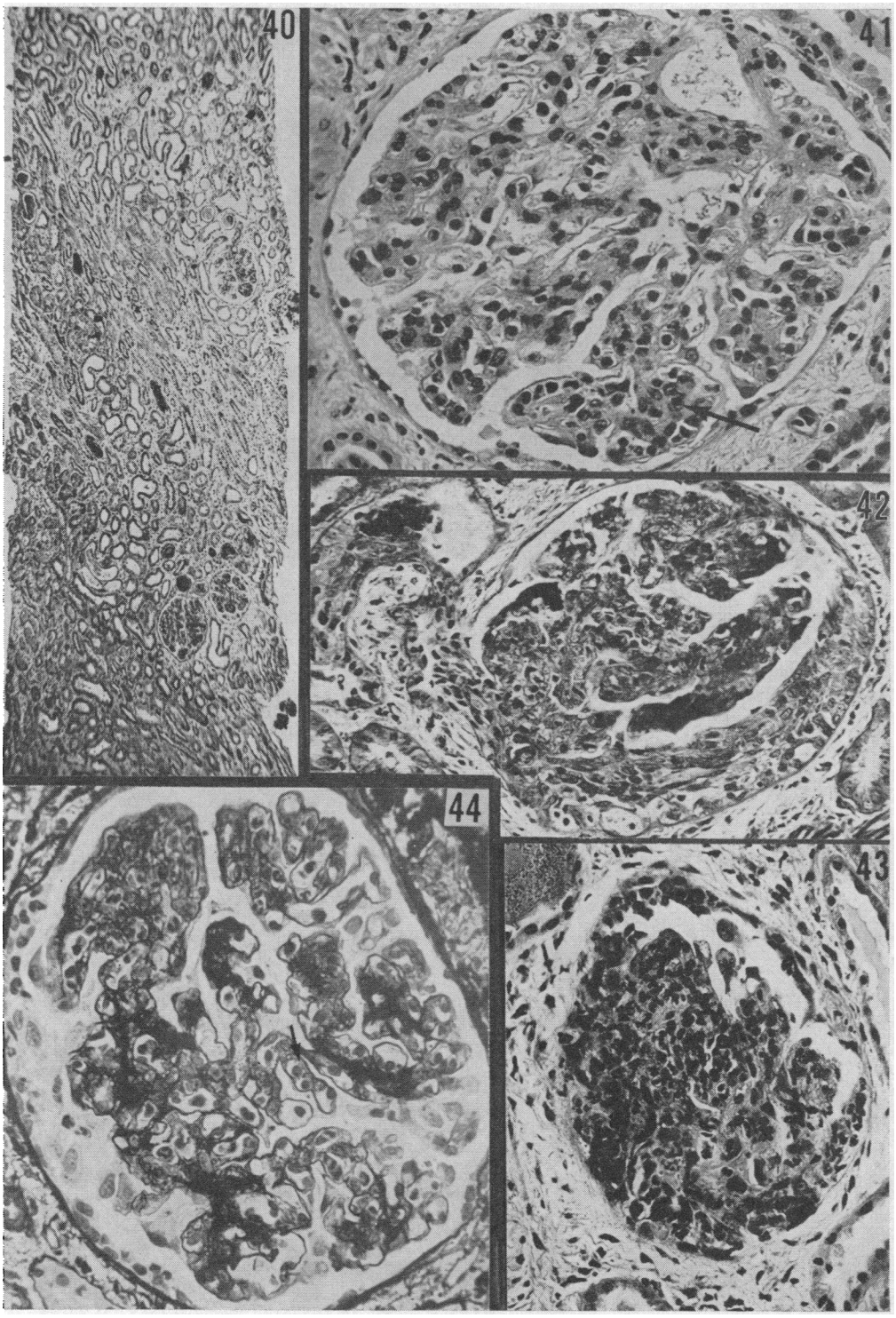
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FIG. 45. CAL. This low-power micrograph shows 2 glomeruli and the interstitial tissue from the most severe acute exudative glomerulonephritis observed in this series. This patient is described in detail in the protocols as Case 7. The biopsy was obtained 30 days after onset and 2 days prior to death. The glomeruli are markedly hypercellular and contain crescents. The interstitial tissue is edematous and contains focal collections of polymorphonuclear neutrophiles and lymphocytes. The proximal tubules are widely separated by edema. At autopsy this kidney weighed 400 g (2μ, H & E, $120\times$).

FIG. 46. CAL. A higher-power view of the right-hand glomerulus in Figure 45, which shows that the hypercellularity is due to numerous polymorphonuclear neutrophiles in the capillary loops and to 3 foci of epithelial cell proliferation (crescents) indicated by the arrows. This is an example of almost pure acute exudative glomerulonephritis. There is no increase in the number of endothelial cells in this glomerulus in the other glomeruli in the biopsy (2μ, H & E, $276\times$).

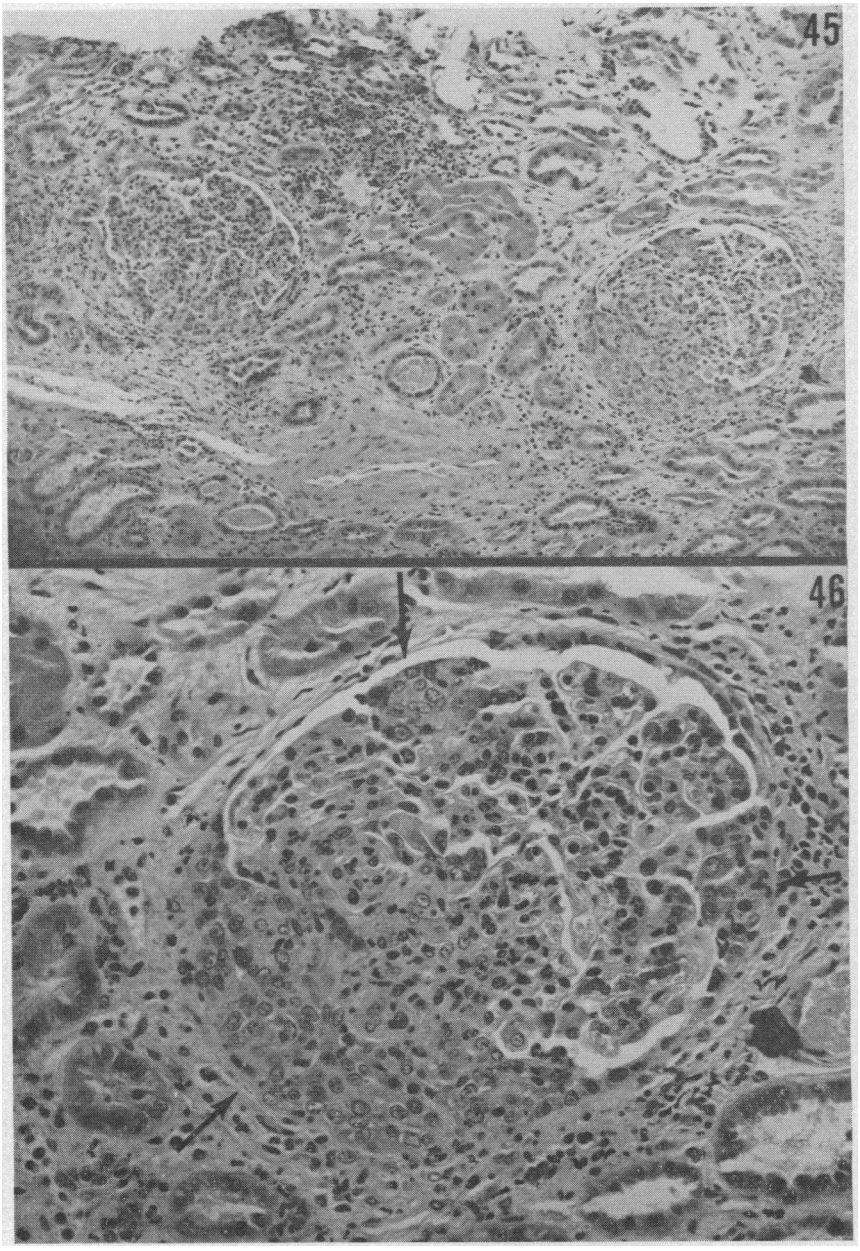
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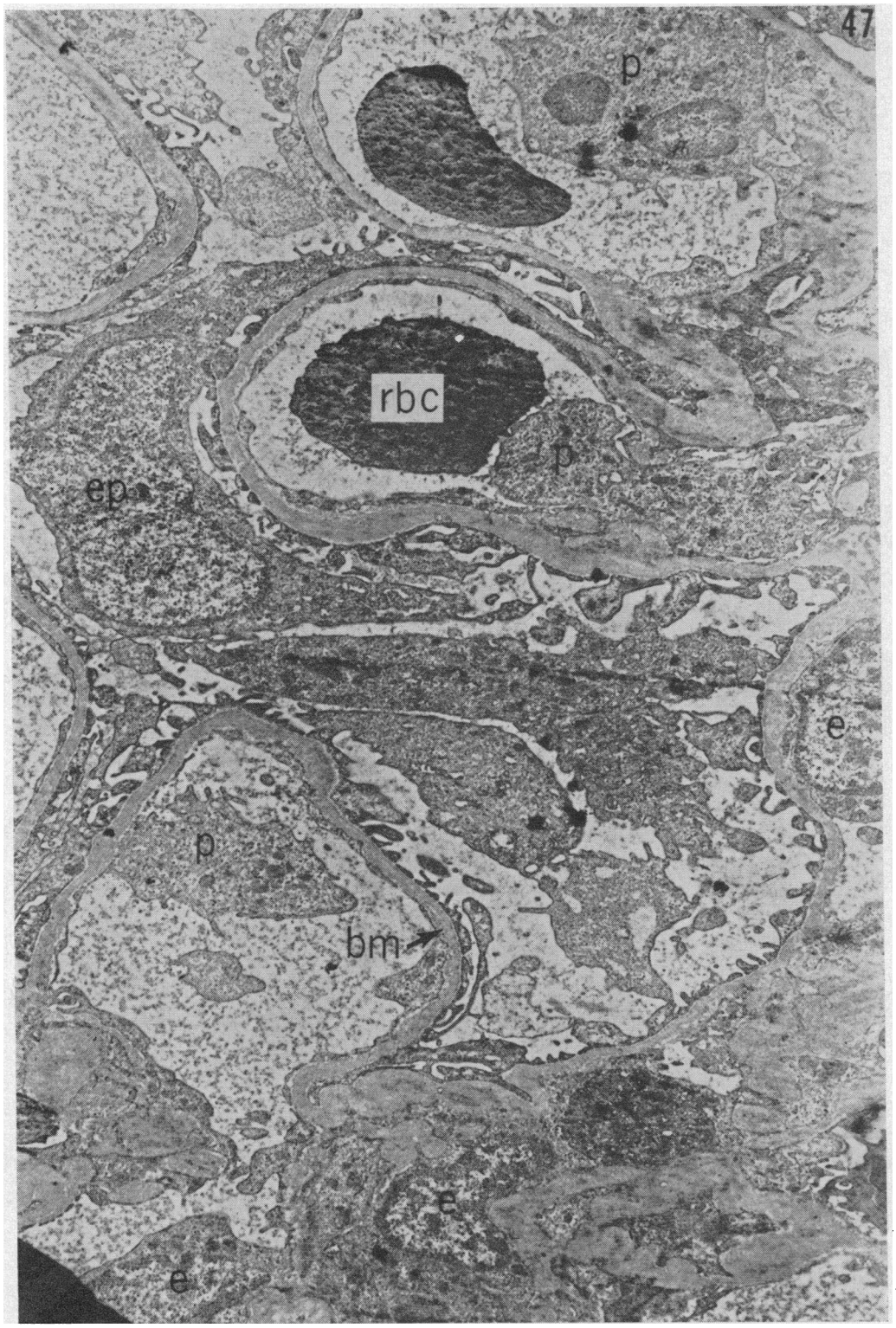
FIG. 47. CAL. This micrograph shows a portion of a glomerulus from the same patient of Figure 46. An epithelial cell (ep) is at upper left center. The epithelial cell foot processes cover the basement membrane but, except for being less dense than normal in some areas, are not remarkable. The basement membranes (bm) are intact, and the endothelial layer covering the membrane internally is slightly swollen. Attached to the endothelium are several polymorphonuclear neutrophiles (p). Two erythrocytes (rbc) are in the lumens of the capillaries. Four nuclei (e) of mature endothelial cells are noted (7,000 ×).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p
rbc
p
ep
e
p
bm
e
e

FIG. 48. APE, SECOND BIOPSY. This patient was first discussed in Figure 40; the second biopsy was obtained 69 days after onset and 47 days after the first biopsy; at this biopsy her urine contained 2+ protein and 10 to 15 erythrocytes; BUN was 38, blood pressure 140/100. Note that the proximal tubules are widely separated by fibrous tissue and that most of the tubular epithelium is flattened and cuboidal (regenerative or atrophic type epithelium). Some normal proximal tubules are adjacent to the glomerulus on the upper right. The capillary loops of the glomeruli are widely patent (2μ, CT, 166×).

FIG. 49. APE, SECOND BIOPSY. Another glomerulus from the same patient of Figure 48. The lobular stalks are slightly thickened and hypercellular and the capillary loops are free of inflammatory cells (2μ, H & E, 436×).

FIG. 50. APE, SECOND BIOPSY. Another glomerulus from the same patient of Figure 48. Note the lobular scar and adhesion on the right (6μ, PAS, 356×).

FIG. 51. COL, FIRST BIOPSY. Glomerulus from biopsy obtained 66 days after onset in a 39 year old man (Case 8 in the protocols). At the time of this biopsy his urine contained 2+ protein and 10 to 15 red cells; BUN was 14, blood pressure 142/100. This glomerulus shows part of a healed crescent and a scarred lobule at the lower right, a relatively normal lobule at lower left and lobules with varying amounts of lobular stalk thickening and hypercellularity elsewhere in the glomerulus. The surrounding tissue (not illustrated in figure) was normal (2μ, PAS, 480×).

FIG. 52. COL, SECOND BIOPSY. Glomerulus biopsy obtained 197 days after onset from patient of Figure 51. His urine contained a trace of protein and no red cells at this time; BUN was 15, blood pressure 128/78. Most of the glomerulus is hyalinized and adherent to Bowman's capsule (2μ, CT, 520×).

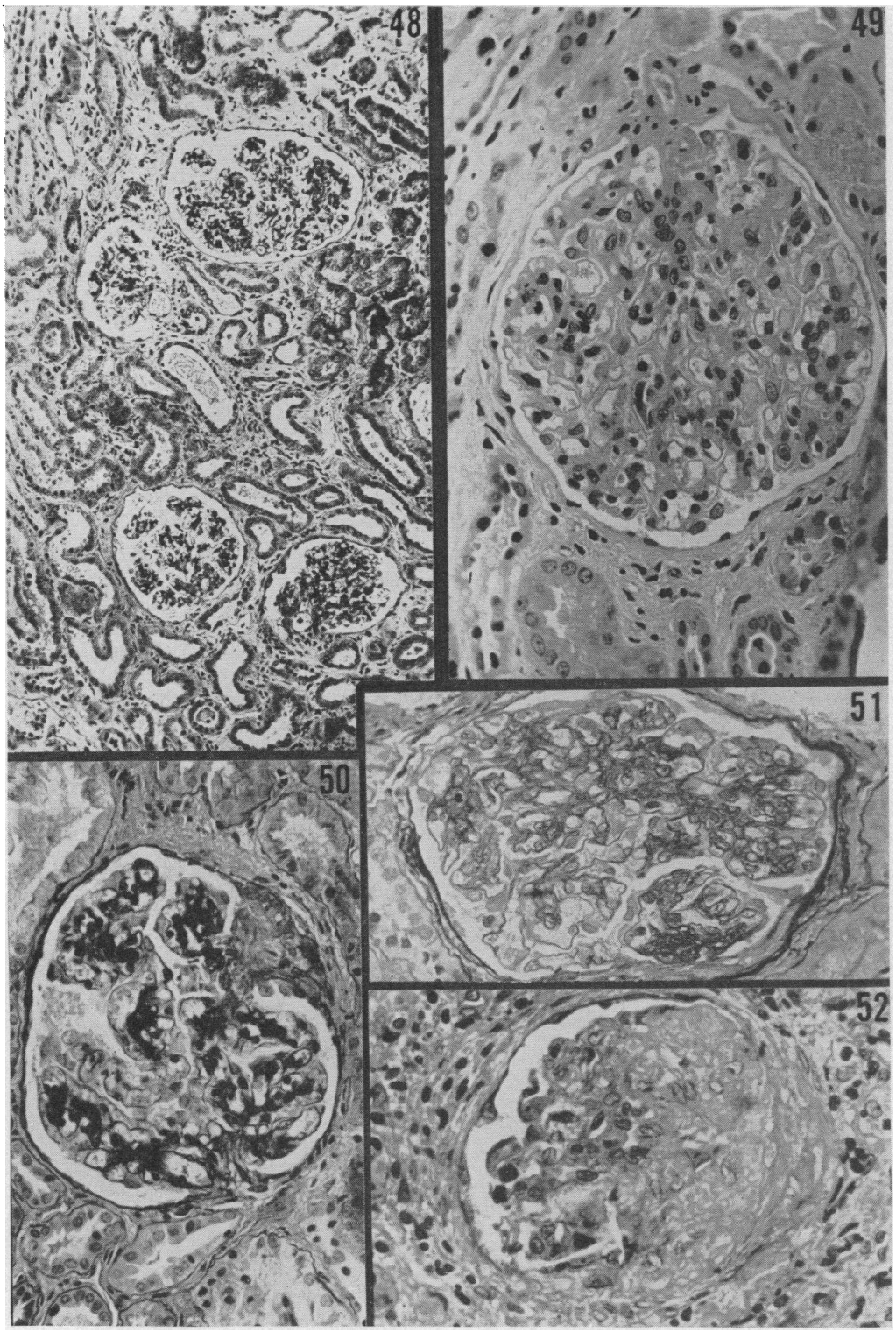
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FIG. 53. ROB. Low-power view of area of interstitial fibrosis from biopsy obtained 97 days after onset in a 20 year old white male. At this time his urine contained 1 + protein and 50 to 100 red cells; BUN was 24, blood pressure 120/80. Note that both glomeruli in the figure (arrows) show lobular scarring and partial hyalinization and that the cortex is largely replaced by dense collagenous tissue. Glomeruli from a less scarred area are shown in Figure 55 (6μ, CT, 164 $\times$).

FIG. 54. ROB. High-power view of a scarred glomerulus from general region illustrated in Figure 53. Note that almost every capillary loop is obliterated (6μ, CT, 450 $\times$).

FIG. 55. ROB. Two glomeruli from a much less scarred portion of the biopsy than that illustrated in Figures 53 and 54. The tubules are separated by an increased amount of interstitial fibrous tissue. Both glomeruli show the lobular stalk thickening and hypercellularity characteristic of the subsiding phase of proliferative glomerulonephritis. This patient presumably had a mixed initial histopathologic picture in which there was sufficient focal exudation in some glomeruli to yield the scarring shown in Figures 53 and 54, superimposed upon a primarily proliferative response (2μ, H & E, 324 $\times$).

FIG. 56. COL, THIRD BIOPSY. Normal glomerulus from patient illustrated in Figures 51 and 52. This biopsy was obtained 51 months after onset and 18 months after the proteinuria had disappeared (2μ, H & E, 280 $\times$).

FIG. 57. COL, THIRD BIOPSY. Another glomerulus from the same biopsy of Figure 57. This glomerulus shows on the left an adhesion of a glomerular capillary loop to Bowman's capsule and hypercellular thickened lobular stalks, 3, 10 and 11 o'clock (2μ, H & E, 280 $\times$).

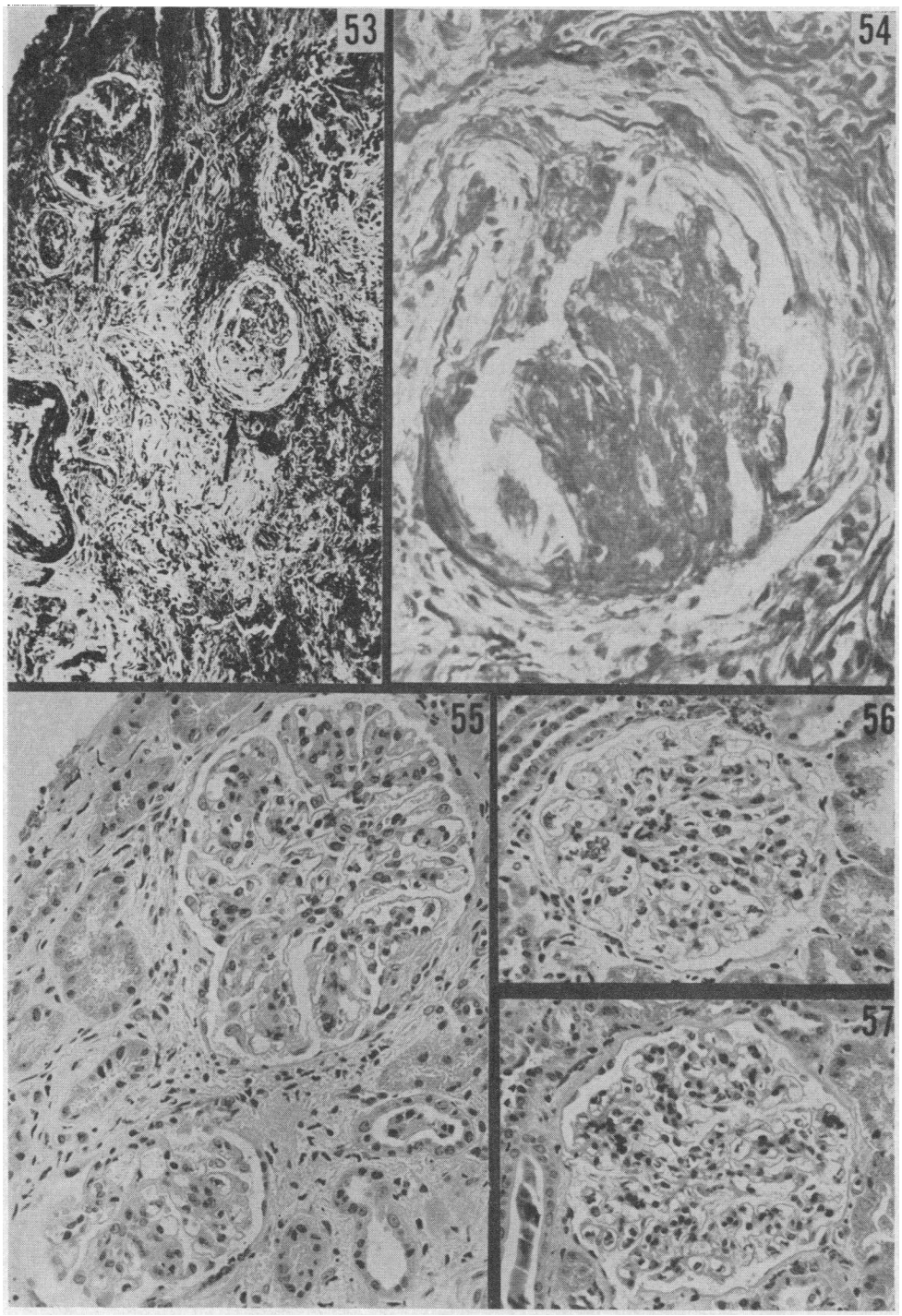
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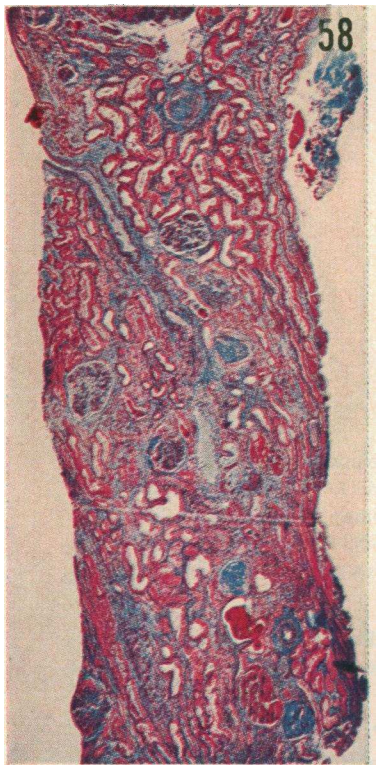
FIG. 58. VLA, FIRST BIOPSY. Low-power view of biopsy obtained 82 days after onset from a 37 year old white male. His urine contained 1+ protein and many red cells at the time of biopsy; BUN was 45, blood pressure 138/100. Note the diffuse disruption of cortical architecture by interstitial fibrous tissue. Several hyalinized and partially hyalinized glomeruli are visible (2μ, CT, 55×).

FIG. 59. VLA, FIRST BIOPSY. High-power view of glomerulus at very upper left in Figure 58. Note the lobular scar and healing crescent involving most of the lower right-hand side of the glomerulus. The remaining glomerular lobules are within normal limits. The cortex adjacent to this glomerulus is fibrotic and contains few tubules (2μ, CT, 350×).

FIG. 60. VLA, FIRST BIOPSY. High-power view of a glomerulus from the biopsy of Figure 58. The silver stain shows that most of the capillary loops are widely patent and that the basement membranes are of normal thickness. The stalks of most of the lobules of the glomerulus, particularly those at 2 and 3 o'clock, are thickened. Note the adhesion at 4 o'clock. This is filled with silver-positive collagen fibrils. The thick black line running to the lower right of the photograph is caused by a fold in the section (2μ, PAS-methenamine with hematoxylin counterstain, 554×).

FIG. 61. VLA, FIRST BIOPSY. Another glomerulus from the biopsy of Figure 58. The lobules at the arrows are thickened and hypercellular (2μ, CT, 346×).

FIG. 62. VLA, SECOND BIOPSY. Almost normal glomerulus from a biopsy obtained 162 days after onset and 80 days after the first biopsy from the same patient of Figures 58–61. His urine contained 1+ protein and occasional red cells at this time; BUN was 27, blood pressure 120/72 (2μ, H & E, 532×).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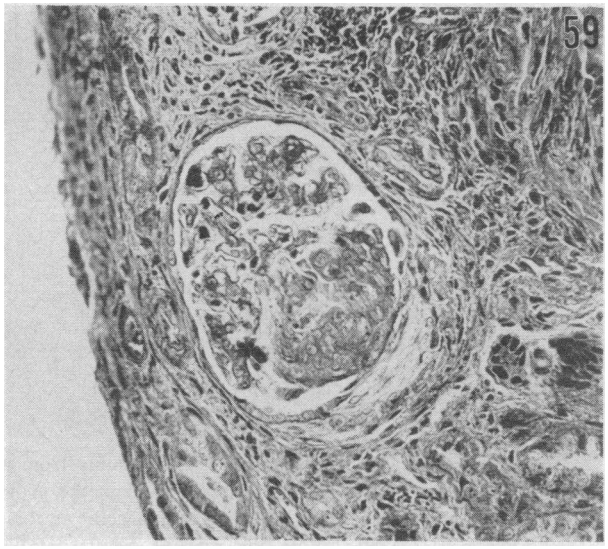
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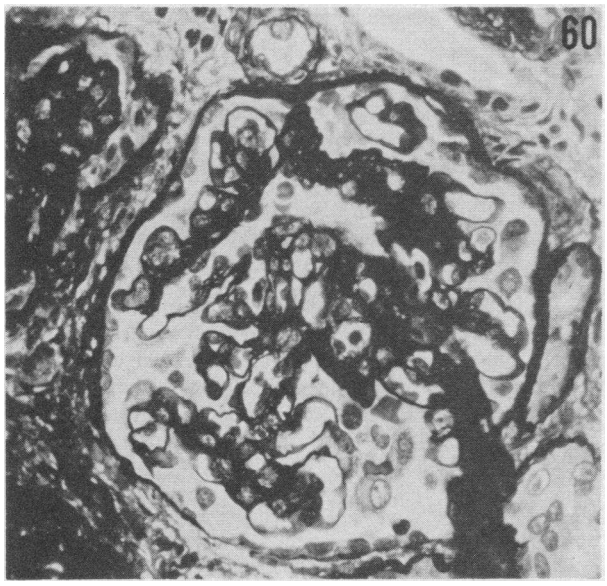
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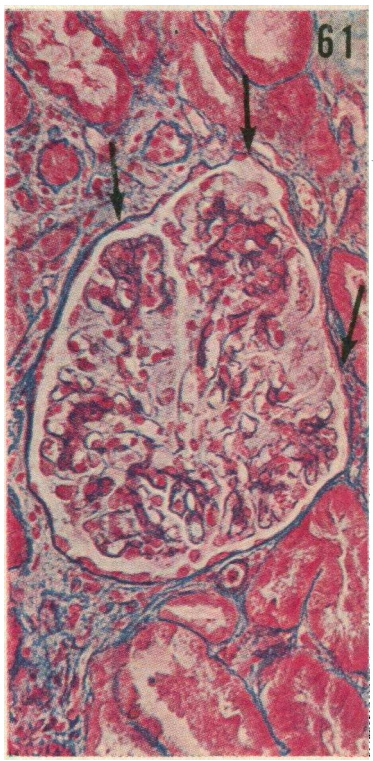
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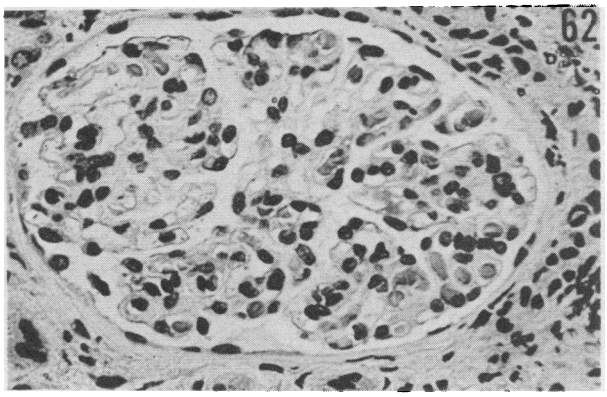
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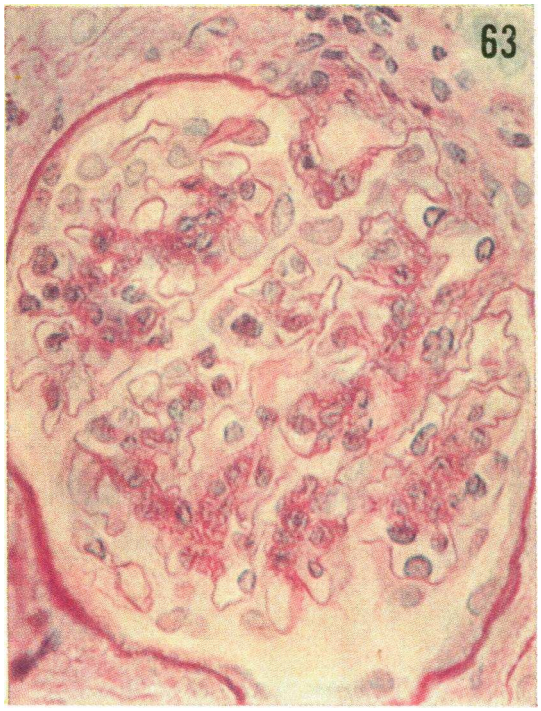
FIG. 63. TRA, FIRST BIOPSY. Glomerulus from a biopsy from a 19 year old white male 71 days after onset (Case 5 in the protocols). The urine contained 1+ protein and occasional red blood cells at this time; BUN was 13, blood pressure 135/80. Note the marked lobular stalk thickening and hypercellularity; basement membranes and arterioles at the hilus are normal (2μ, PAS, 512×).

FIG. 64. TRA, FIRST BIOPSY. Severely diseased glomerulus from biopsy of Figure 63. Note the healing crescents at the bottom and upper left. The lobular stalks show thickening and hypercellularity. The lobules adjacent to the crescents are obliterated and adherent (2μ, PAS, 840×).

FIG. 65. SHI. Normal glomerulus obtained in biopsy 120 days after onset, and 2 days after disappearance of proteinuria in a 20 year old male; Case 10 in protocols (2μ, PAS, 525×).

FIG. 66. SHI. Another glomerulus from patient of Figure 65. This biopsy showed both diseased and normal glomeruli. This is the most severely diseased glomerulus found. A healing crescent with a scarred glomerular lobule adherent to it is visible on the left. A few other glomeruli showed occasional thickened hypercellular lobules similar to that at 3 o'clock in this glomerulus (2μ, PAS, 525×).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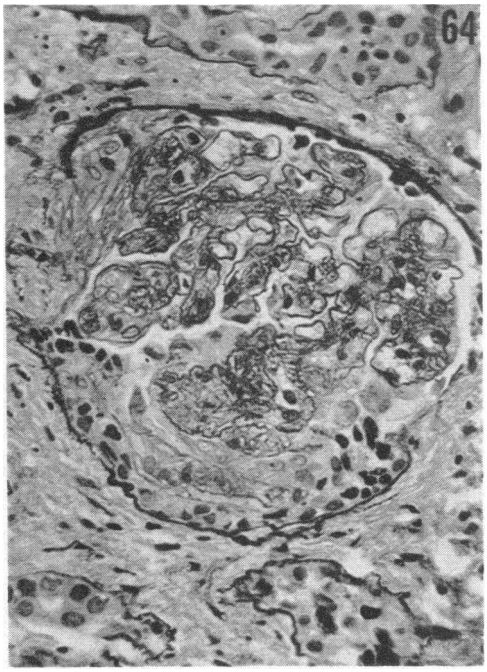
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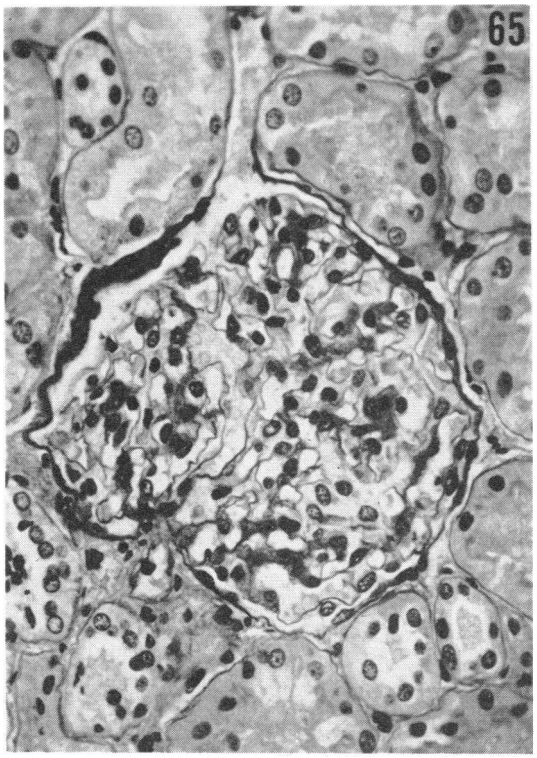
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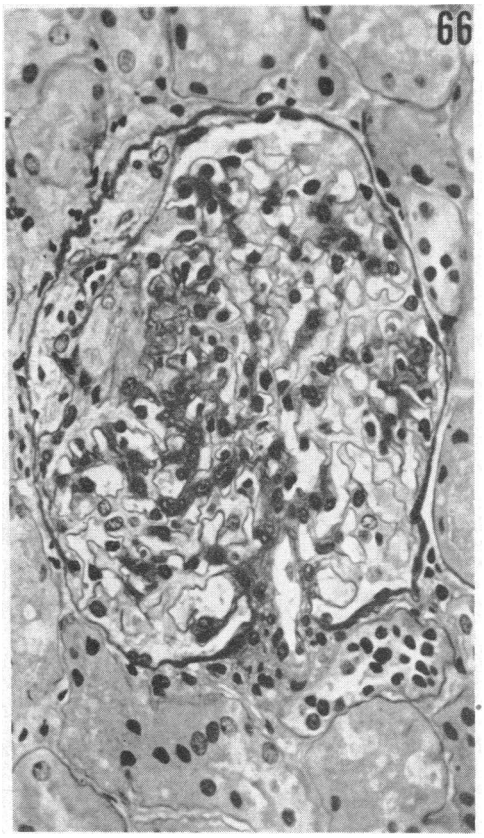
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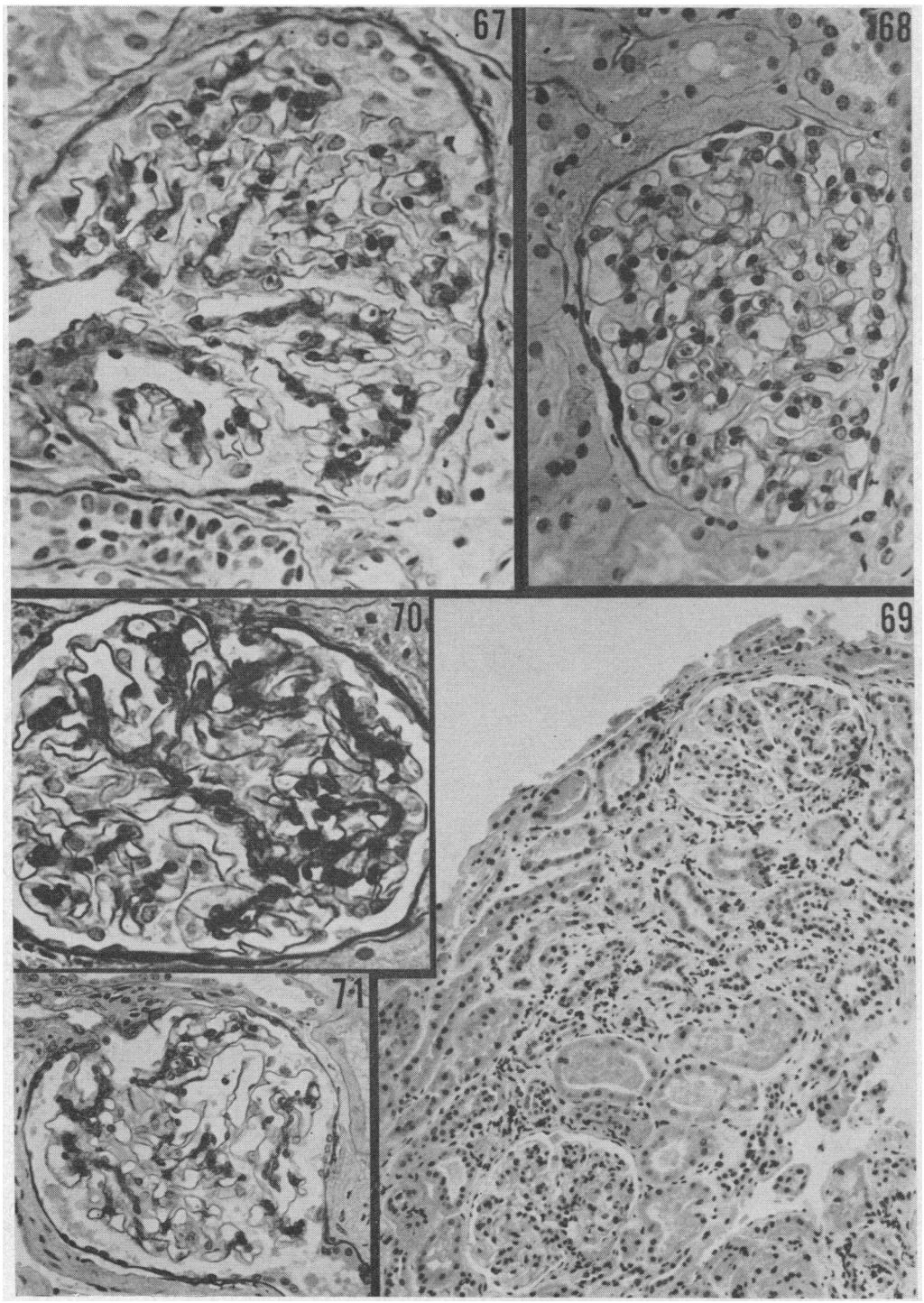
FIG. 67. SWI, FIRST BIOPSY. Normal glomerulus from first biopsy obtained from a 19 year old man 32 days after onset (Case 9 in the protocols). This patient's disease was diagnosed by laboratory findings only. At this biopsy his urine contained a trace of protein and occasional red blood cells; BUN was 12, blood pressure 140/60. A crushing artifact that commonly occurs in needle biopsies of kidney is well illustrated by this glomerulus. The basement membranes of some of the capillary loops are wrinkled, having been squashed together by the trauma of forcing the cortical tissue into the biopsy needle. This phenomenon is more common in normal than in abnormal kidneys. Swollen or fibrotic kidneys usually do not show much crushing of glomeruli or tubules except along the cut edge of the tissue (2μ, PAS, 825 ×).

FIG. 68. ROS. A representative normal glomerulus from a biopsy obtained 17 days after onset of disease in a 20 year old white male. His urine showed no protein and 10 red cells at this time; BUN was 15, blood pressure 120/70 (2μ, PAS, 450 ×).

FIG. 69. JAM, FIRST BIOPSY. Low-power view of kidney from a 26 year old Negro male biopsied 28 days after onset. His urine showed a trace of protein and a few red cells at this time; BUN was 19, blood pressure 134/90. The interstitium is fibrotic and contains an infiltrate of chronic inflammatory cells and a few polymorphonuclear neutrophiles. The glomeruli are not hypercellular and show no signs of exudation. The endothelial nuclei are all small and have dense chromatin (2μ, H & E, 234 ×).

FIG. 70. JAM, FIRST BIOPSY. High-power view of another glomerulus from the patient of Figure 70. Note that basement membranes are normal, the glomerulus is not hypercellular and that it is free of inflammatory cells (6μ, PAS, 510 ×).

FIG. 71. JAM, SECOND BIOPSY. Glomerulus from second biopsy obtained 1,013 days after onset and 985 days after first biopsy in the patient of Figures 69 and 70. At this time his urine contained 2+ protein and no erythrocytes; BUN was 14, blood pressure 150/90. This glomerulus is representative and is not abnormal (2μ, PAS, 282 ×).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