

Primary Proliferative Glomerulonephritis - A Clinicomorphological Analysis

Pages with reference to book, From 56 To 65

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Abstract

A clinicomorphological break down of 278 cases of various types of proliferative glomerulonephritides is discussed. All these patients presented with the clinical features of nephrotic syndrome with or without haematuria. The most common cause of nephrotic syndrome was diffuse proliferative glomerulonephritis (33.75%). The age range of these patients was 6 to 50 years with male being the dominant sex. These cases were received between 1968 and 1981 (JPMA 33 56-,1983).

Introduction

Primary renal glomerular diseases have so far not been classified, however during the last decade the terminology of various types of primary glomerular diseases has almost been specified. In addition, they have been divided into two broad but distinct groups of proliferative and non-proliferative lesions. This is largely due to a wide spread application of histochemical, electron microscopic and Immunofluorescent techniques in the study of morphology and to some extent the pathogenesis of nephritis. In view of the availability of new and powerful treatment modalities, it has become increasingly important to define more precisely both the type and stage of progression of disease. This type of diagnostic discrimination will undoubtedly help in the prevention and reversal of these diseases and increase our understanding of the mechanisms involved in primary renal disease i.e. glomerulonephritis. Since the introduction of renal biopsy technique on human kidney (Iversen and Brun, 1951) numerous clinicopathological studies have been performed to elaborate upon the various aspects of nephritis (McGovern, 1964; Pollak et al., 1968; White et al., 1970; Heptinstall, 1974; Kashgarian et al., 1977; Jenis and Lowenthal, 1978; Meadows, 1978; Davison, 1981). Newer techniques in microscopy and immunology have furnished the means for characterizing individual renal lesions from their initial to terminal phases. In this paper it has been attempted to utilize this information in classifying and describing different types of proliferative nephritis in 403 of the cases of primary glomerulonephritis studied during the past 12 years. It does not include the nonproliferative primary lesions which will be discussed in a separate communication.

Material and Methods

Renal Biopsies:- A total of 278 biopsies from patients with primary proliferative glomerulonephritis were examined. Each tissue was fixed in 10% formal saline, dehydrated in ascending grades of ethanol, cleared in xylene and cut into 4 - 5 U thick sections after making paraffin blocks. These sections were stained with Haematoxyline and eosin; periodic acid Schiff's reaction and Methenamine silver stains. In a total of 278 biopsies 210 were also examined by electron microscope. Fluorescent microscopy was performed on 168 biopsies.

After these structural studies all the biopsies were divided into various morphological types using an accepted nomenclature for each type.

Patients and Laboratory investigations

In a total of 459 biopsies received, 403 were found to have primary glomerulonephritis; whereas 56

showed nephritis associated with various systemic disorders. The 403 biopsies included 278 cases of proliferative nephritis and 125 cases of nonproliferative nephropathies.

All patients were investigated for renal functions, Urinary proteins, total serum protein, Albumin and Globulin, Serum creatinine B.U.N., Serum total cholesterol, E.S.R. and evidence of urinary tract infection. Antistreptolysin-O titer could be carried out in only 198 patients. These investigations were followed by radiological assessment of renal functions. The renal biopsies were performed, using either an open method by exposing the kidney, or the percutaneous route with a Menghini's or modified Vimsilverman's needle. The renal tissues obtained after open biopsies, were processed for light, electron and immunofluorescent studies; whereas those obtained after needle biopsy procedure were processed for light microscopy except 30 biopsies which were also processed for electron microscopy.

Results

All the cases (403) of primary glomerulonephritis when studied morphologically, they were divided into various histological types (Fig. 1).

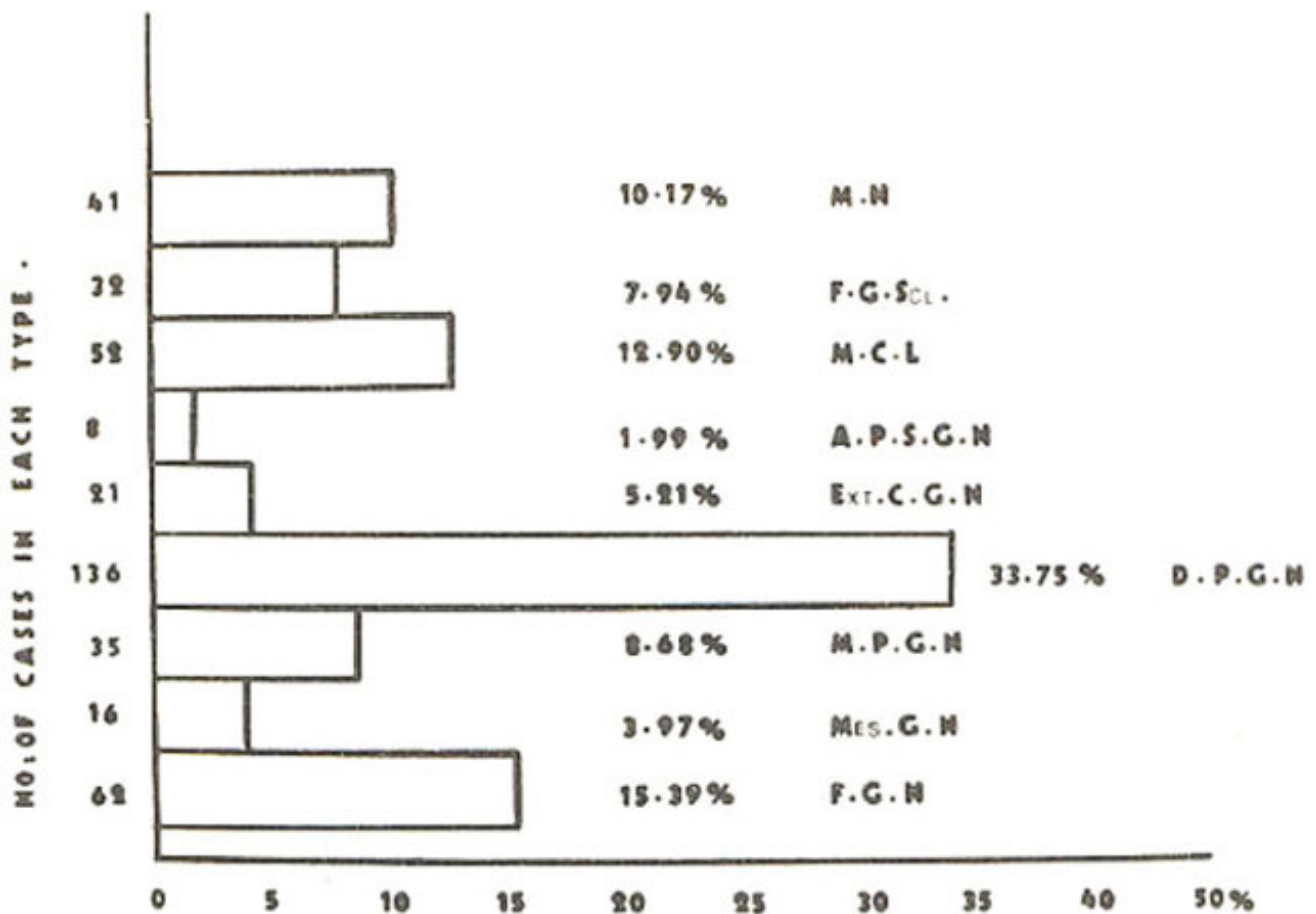


Fig. 1. A breakdown of 403 biopsies of primary glomerular lesions into various morphological types. G.N. = Glomerulonephritis; M.N = Membranous Nephropathy; F.G.Sc. = Focal glomerular Sclerosis; M.C.L. = Minimal change lesion; A.P.S.G.N. = Acute post Streptococcal G.N., Ext. C.G.N., = Extracapillary G.N.; D.P.G.N. = Diffuse proliferative G.N; M.P.G.N. = Membranoproliferative G.N; Mes. G.N. = Mesangial G.N.; F.G.N. = Focal glomerulonephritis.

The commonest amongst them was diffuse proliferative glomerulonephritis (33.75%). As regards the sex ratio, male was the dominating sex with a male: female ratio of 2:1 (Fig. 2).

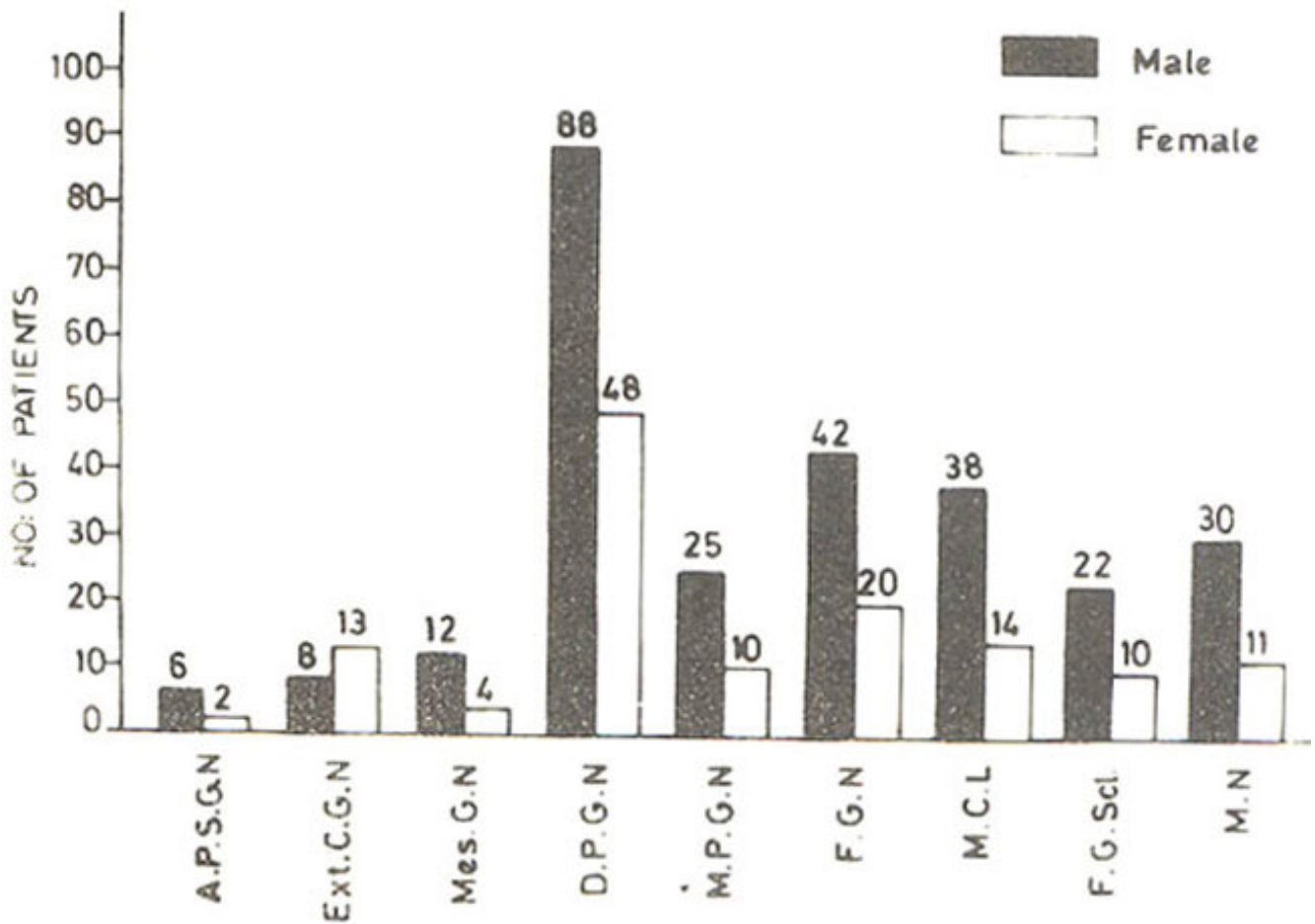


Fig. 2. Sex distribution in various types of primary glomerular diseases in 403 patients.

The age range in these patients was 4 -52 years; with the maximum number of patients falling in the 2nd and 3rd decades (Fig. 3).

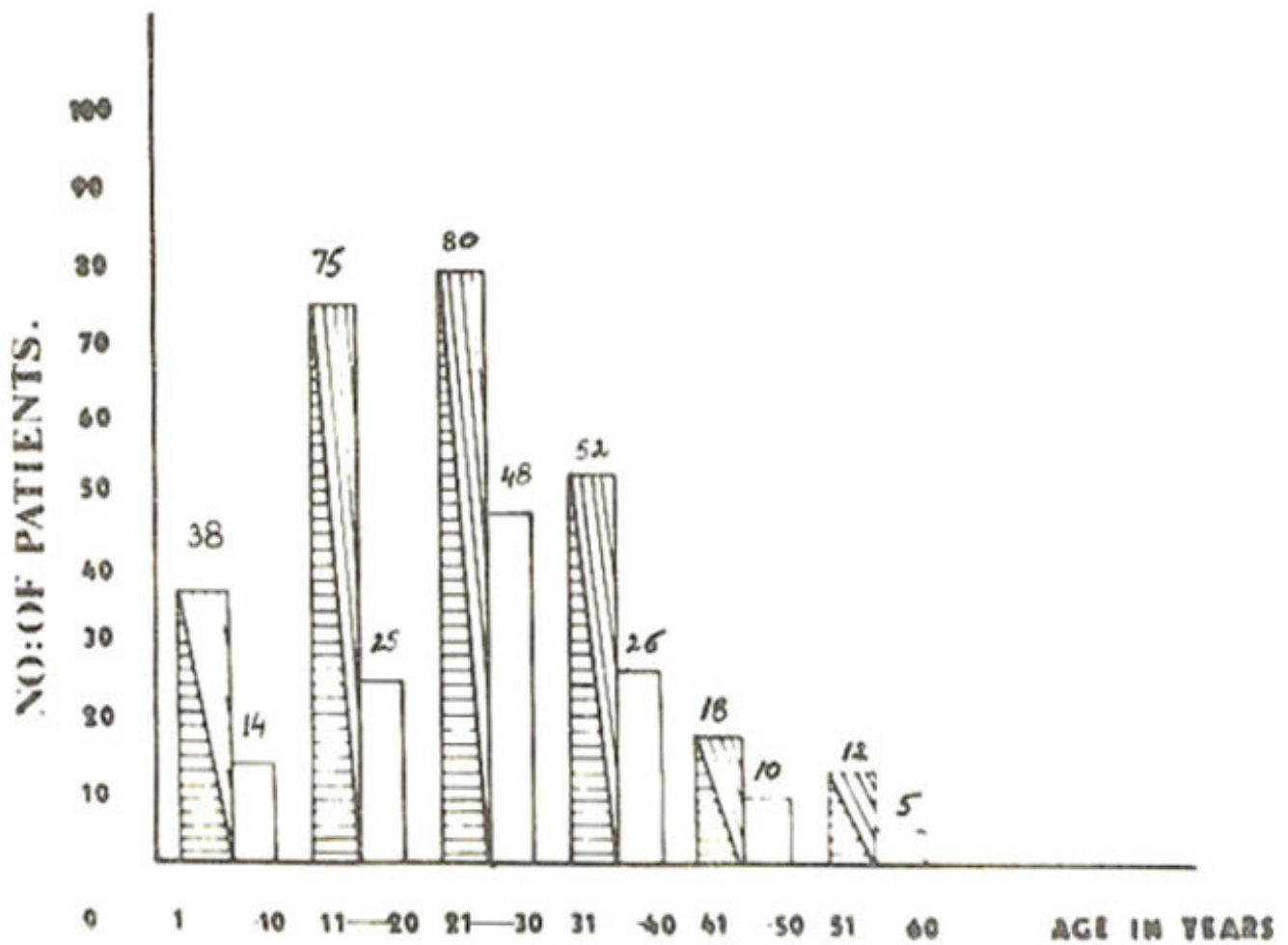


Fig. 3. The age range of 403 patients shown against both sexes.

Acute post streptococcal glomerulonephritis (A.P.S.G.N)

The clinical manifestations of renal disease in 8 cases of acute nephritis were variable. The duration of illness varied from 1 to 3 weeks. A large majority (6) of these patients gave a history of sore throat. A total of 2 patients gave the history of puffiness of face. Four complained of pain in both renal angles; whereas all the 8 cases volunteered the history of macroscopic haematuria. On examination and observation all of them showed microscopic haematuria, whereas only 6 had tenderness in the renal angles. The details of the clinical features and laboratory investigations are given in tables I and II.

Table - 1

Sr. No.	Clinical Features	A.P.G.N. (8 cases)	Ex.C.G.N. (21 cases)	M.G.N. (16 cases)	D.P.G.N. (136 cases)	M.C.G.N. (35 cases)	F.G.N. (62 cases)
1	2	3	4	5	6	7	8
1.	Age in years	6-16	24-38	18-42	10-50	9-44	12-48
2.	Streptococcal infection	6	4	2	100	2	18
3.	Other infections	1	1	None	10	2	Nil
4.	Oedema-Face	2	8	16	60	28/4	42
	Ankle	Nil	4	Nil	11	4	16
5.	Generalised	Nil	5	Nil	14	3	2
6.	Haematuria Macro	8	16	4	120	8	52
	micro	8	5	12	52	27	4
7.	B.P. in mm Hg	112/76- 156/90	130/80- 160/92	120/72- 140/80	110/78- 185/110	116/76- 180/100	116/72- 150/90
8.	Duration in weeks	1-3	4-10	10-30	16-52	12-46	20-56
9.	Oliguria	4	18	Nil	32	6	2
10.	Pyrexia	6	7	Nil	8	One	2
11.	Sex-Male : Female	6 : 2	8 : 13	12 : 4	88 : 48	25 : 10	42 : 20
12.	24 Hours urinary out put in ML	400-1350	320-910	910-1400	300-1350	260-980	320-1620
13.	Pain/Tenderness Loin	4/6	4/17	Nil	8/62	Nil/12	8/14

G.N = Glomerulonephritis.

A.P.G.N = Acute Poststreptococcal Glomerulonephritis; Ex. C.G.N = Extracapillary G.N;

M.G.N = Mesangial G.N.

D.P.G.N = Diffuse proliferative G.N; M.C.G.N = Mesangiocapillary G.N; F.G.N. = Focal G.N.

Table - II

Sr. No	Type of Lesion	Urinary Proteins G.M. per 24 hours	Total Serum Protein g%	Serum Albumin and Globulin g%	Creatinine Clearance ML/min	Blood Urea mg%	Serum Total Cholesterol mg%	AsoT, Tod Unit	B.S.R. mm/Hr.	Associated U.T.I. (0-+ + + +)
1	2	3	4	5	6	7	8	9	10	11
1.	A.P.G.N.	3.1-10.5	6.2-7.2	3.8-3.9 2.4 3.3	98-62	28-52	210-288	160-1250	28-48	++ 1/8 cases
2.	Ex. C.G.N.	4.5-15.2	5.2-6.1	2.9-3.1 2.3 3.0	60-24	38-82	220-320	160-1250	36-52	++ in 6/21 cases
3.	M.G.N.	2.3-6.2	5.8-7.0	2.8-3.5 3.0 3.3	88-36	32-68	232-292	12-512	22-36	+ in 2/16 cases
4.	D.P.G.N.	3.8-18.6	4.8-6.5	2.4-3.2 2.4 3.3	80-22	30-62	210-320	160-1285	28-40	++ in 35/136 cases
5.	M.P.G.N.	4.6-16.5	5.5-6.2	2.7-3.2 2.8 3.0	72-18	35-58	262-345	160-512	30-46	++ in 6/35 cases
6.	F.G.N.	2.5-10.2	5.8-6.8	3.0-3.4 2.8 3.4	96-48	22-40	226-292	12-160	16-32	+ in 8/62 cases

G.N. = Glomerulonephritis.
A.P.G.N. = Acute poststreptococcal Glomerulonephritis; Ex C.G.N = Extracapillary G.N; M.G.N. = Mesangial G.N.
D.P.G.N. = Diffuse proliferative G.N; M.C.G.N = Mesangiocapillary G.N; F.G.N = Focal G.N:

On microscopical examination the severity of lesion varied. However, they all showed swelling of the glomerular tufts. The dilated capillaries contained numerous leucocytes. In addition to the endothelial cell swelling and proliferation, there was a prominent centrolobular mesangial cell proliferation with swelling and accumulation of increased matrix material. The glomerular basement membrane (GBM) was irregular along its inner surface (Fig. 4).

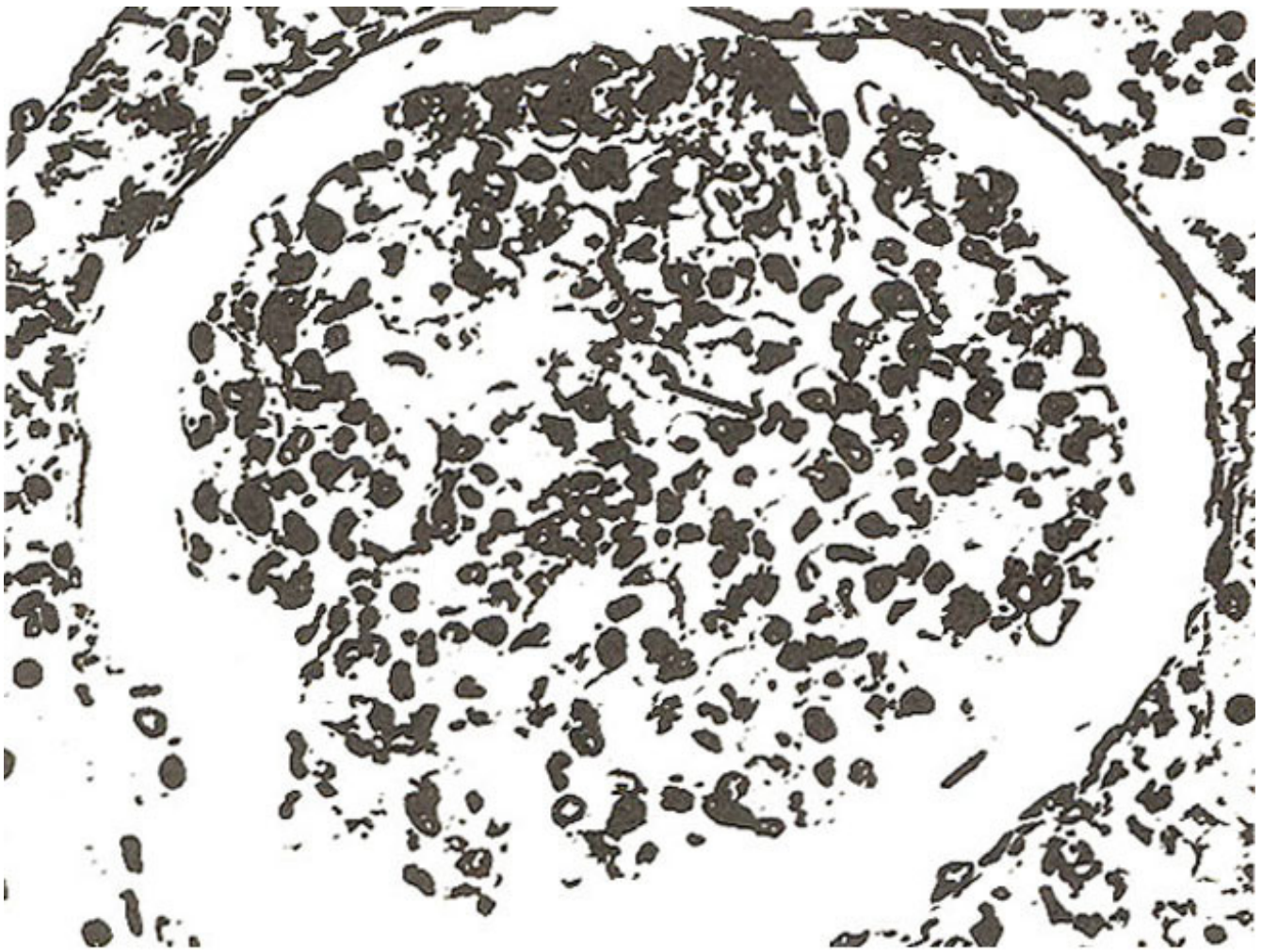


Fig. 4. A glomerulus showing prominence of endothelial cells. Note the polymorph neutrophils (arrow). Hematoxyline and eosin (H&E) X 430.

The electron microscopic examination was carried out on 6 biopsies. It showed conspicuous electron-dense deposits in the mesangial and subendothelial areas. In addition finely granular electron dense humps were also found between the GBM and the epithelial cells (Fig. 5).

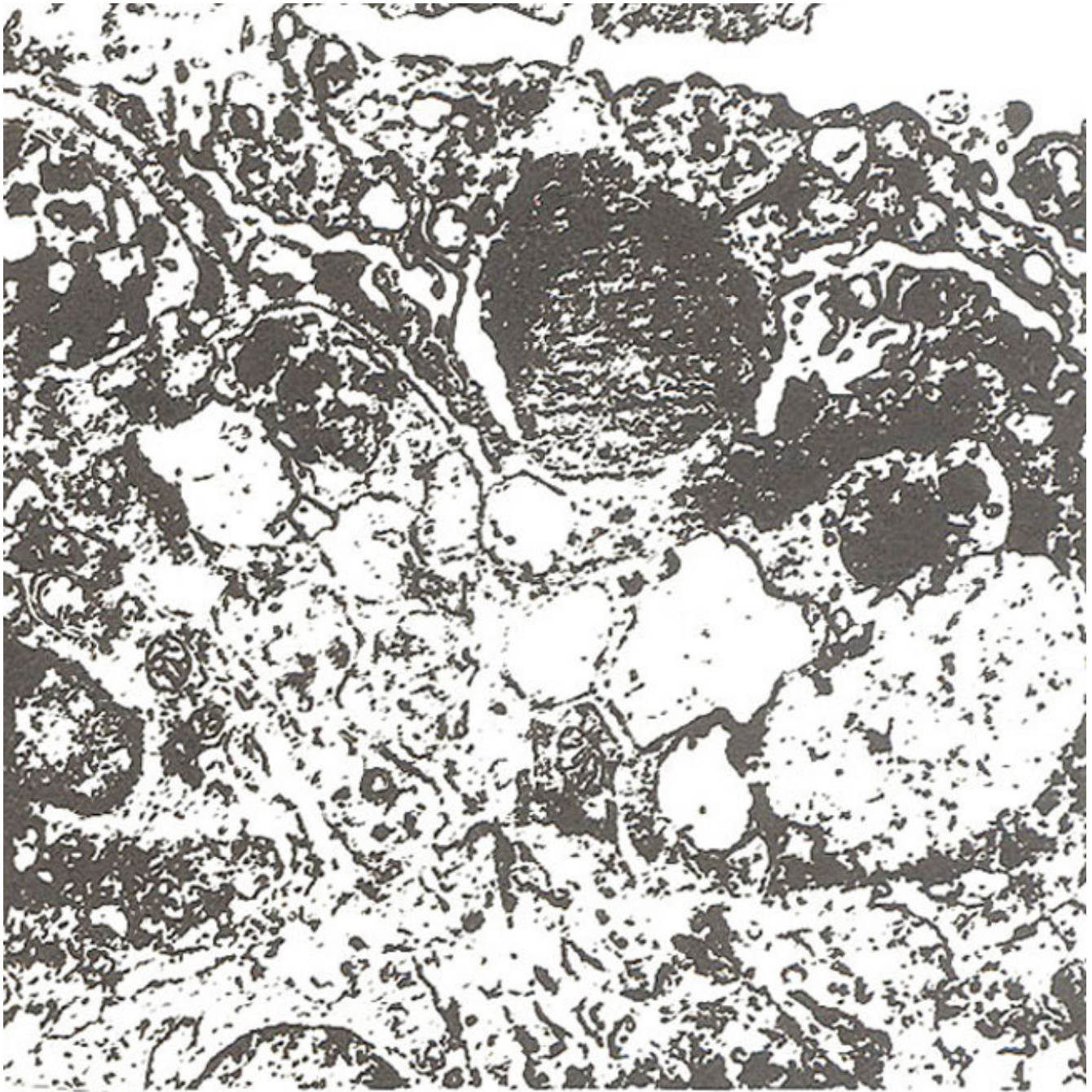


Fig. 5. Portion of a glomerular loop showing a electron dense epithelial hump (arrow). Electron micrograph X 6000.

The epithelial cells showed fusion of the foot processes over the humps.

Immunofluorescent studies were performed on only six biopsies. The deposition of IgG and complement (C3) component was demonstrated along the periphery of the capillary loops and the mesangium.

In a total of 8 cases of acute glomerulonephritis (G.N) studied during the past 12 years; one showed a fulminant inflammation associated with crescent formation, one came in the latent stage of acute GN; whereas the remaining showed changes typical of acute poststreptococcal G.N.

Extra capillary glomerulonephritis (Ext. C.G.N)

In our series of 278 cases of primary proliferative G.N., 21 were diagnosed as Ext. C.G.N. In 14 of these 21 cases the illness was preceded by an episode of streptococcal infection the onset being essentially that of a severe acute post Strept G.N. The remaining 7 patients showed the clinical picture of nephrotic syndrome (Table I). The laboratory investigations including urinary proteins, creatinine clearance, biQod urea and serum proteins shows gross abnormalities (Table II).

Microscopic examination of most of them revealed identical appearances. In glomeruli the changes occurred in both the tuft and the cells lining the Bowman's capsule. The tuft in 8 cases showed changes of acute G.N. Two of these 8 cases showed adhesions of the tufts to the Bowman's capsule. The most remarkable change in all the cases was an intense extra-capillary cellular proliferation of the epithelial cells of Bowman's capsule which formed epithelial crescents (Fig. 6).

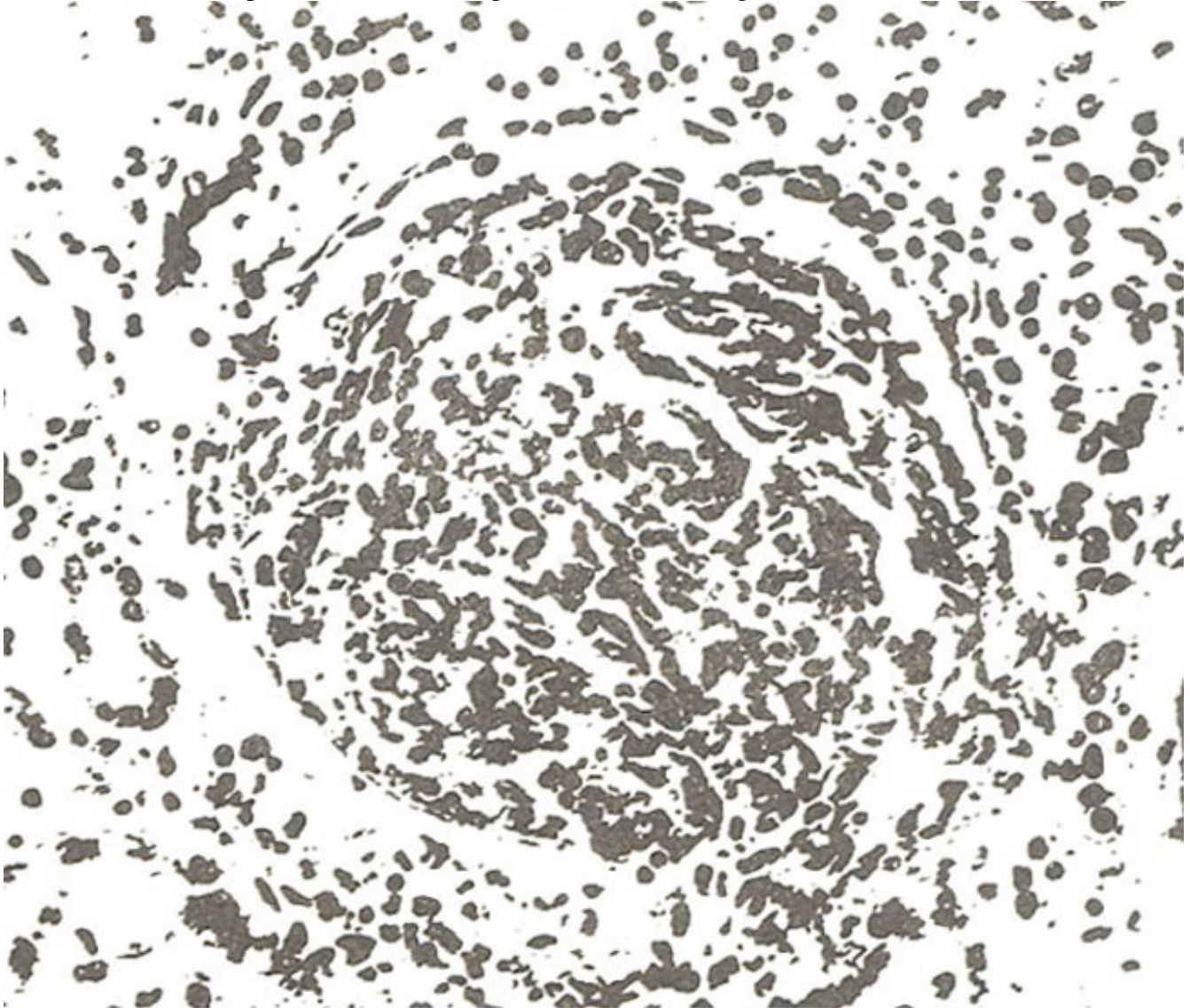


Fig. 6. A glomerulus showing extra capillary epithelial cell proliferation with a crescent formation. H & E. X 350.

Within these proliferating cells were numerous acute inflammatory cells, red cells and fibrin. The

glomerular tufts in most of these cases showed necrosis associated with large deposits of fibrin. The number of glomeruli having undergone crescent formation varied. In 8 cases all the glomeruli showed crescent formation; whereas amongst the remaining, 5 showed 80% crescents; and 4 showed about 50% glomerular crescents. The remaining glomeruli, in them underwent changes of acute G.N. with heavy deposits of fibrin.

The immunofluorescent microscopy was performed on 8 biopsies, three of them shows a pattern similar to what is observed in Poststreptococcal G.N. i.e. deposition of IgG and C3 in the peripheral loops and mesangial region.' In the remaining five biopsies IgG and IgM and C3 were localised in a linear fashion involving all the glomerular loops.

Diffuse proliferative G.N. (D.P.G.N)

In a total of 278 cases of proliferative glomerulonephritis, 136 biopsies showed diffuse proliferative glomerulonephritis (D.P.G.N). Their ages ranged between 10 and 50 years. Male (88) was the dominant sex over female (48). A large majority (100) of them gave an evidence of Streptococcal infections; whereas in 10 cases there was an evidence of other pyogenic infections. A total of 65 patients showed the features of nephrotic syndrome. Haematuria (Micro or macro) with or without oedema was observed in over 85 per cent of patients. Thirty two of those who had nephrotic syndrome, complained of a significant reduction in the 24 hour urinary out put. The details of clinical features and laboratory investigations are shown in tables I and II.

The microscopic examinations revealed that the main features of the glomeruli were diffuse proliferation of mesangial and endothelial cells involving all the glomeruli with an almost equal severity (Fig. 7).

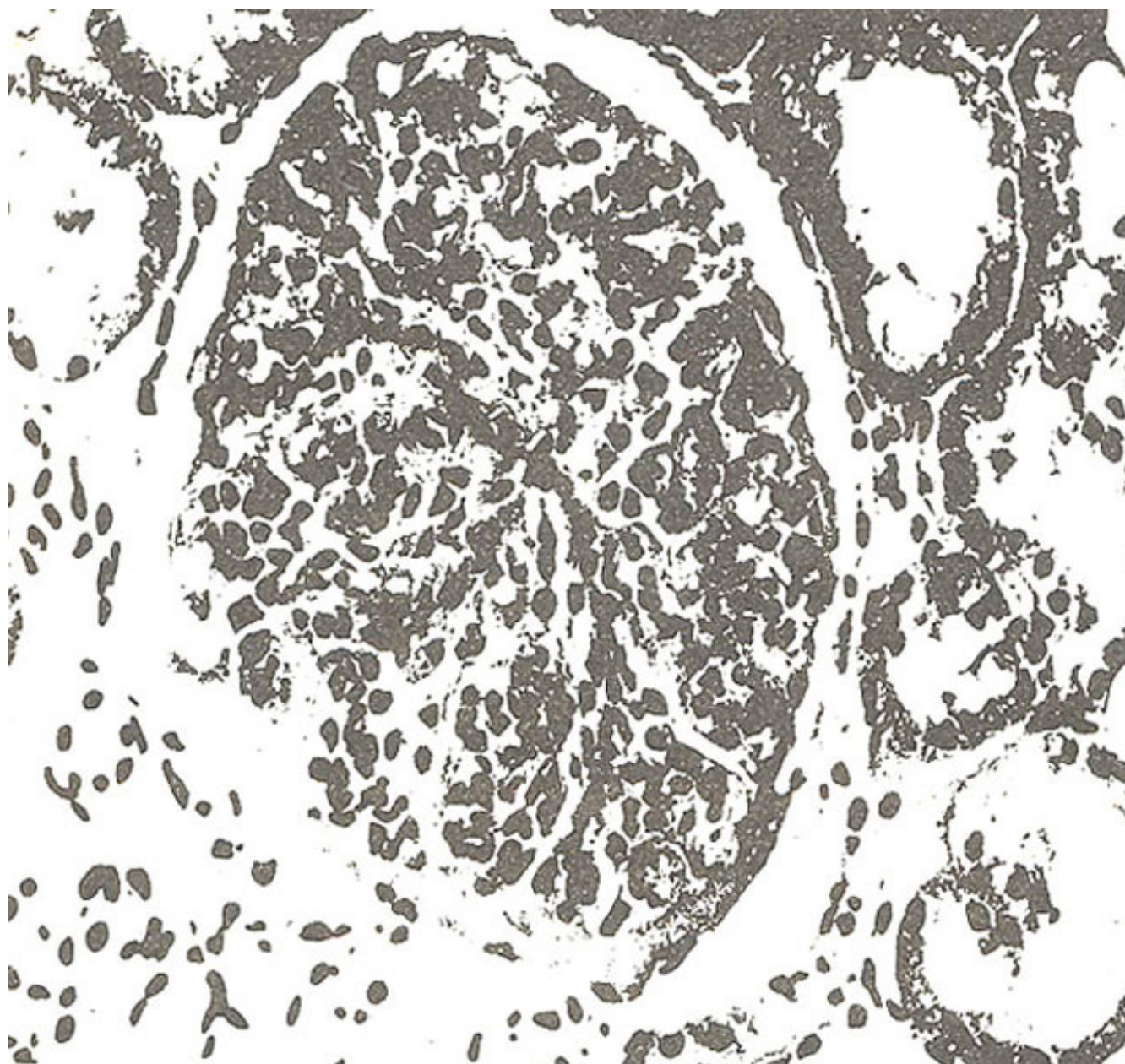


Fig. 7. A glomerulus showing a diffuse proliferation of endothelial and some mesangial cells. H and E. X 350.

Thirty Seven of the 136 biopsies showed a moderate to marked prominence of the glomerular lobules forming the lobular variety of diffuse proliferative glomerulonephritis (Fig.7a).

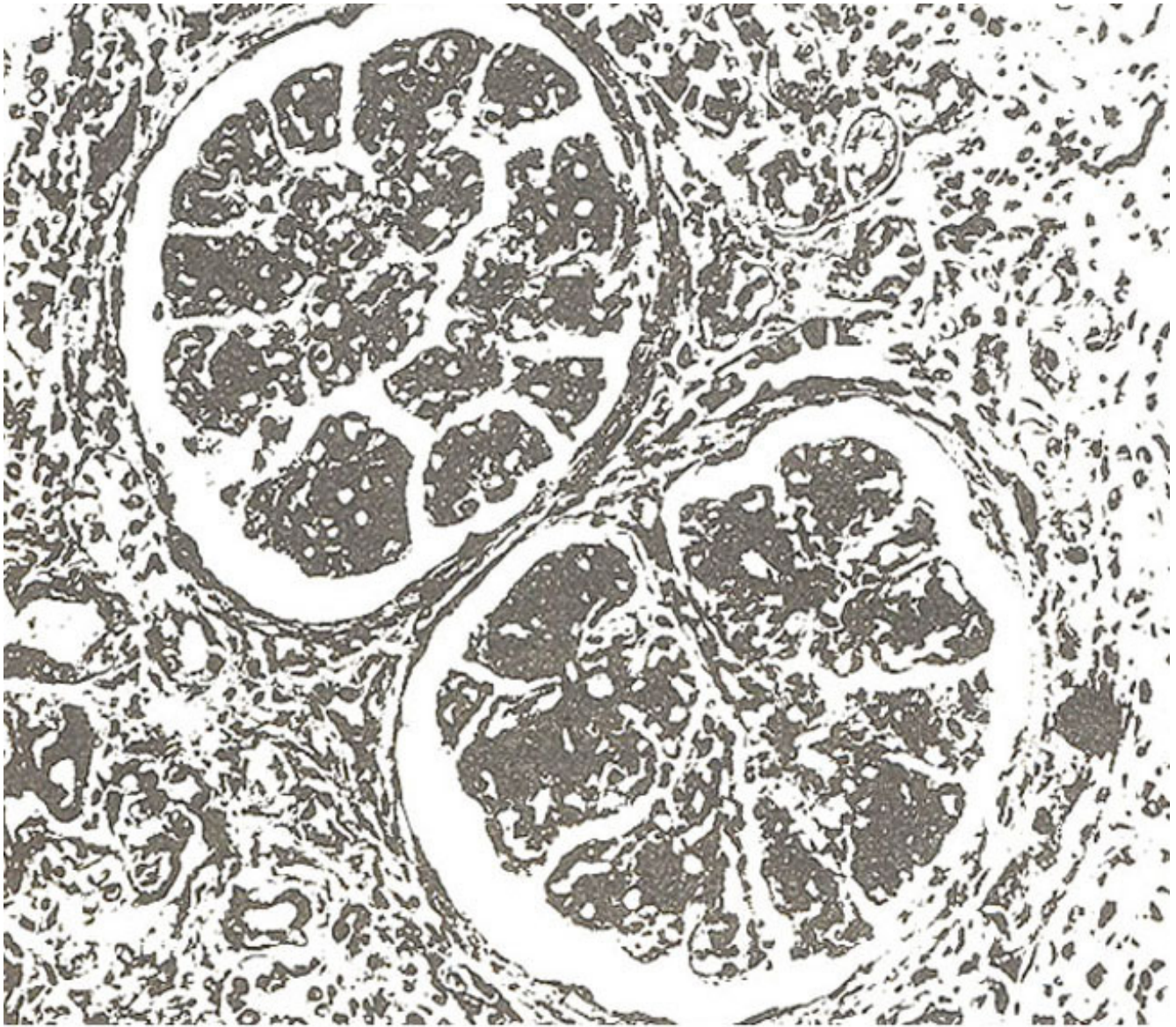


Fig. 7a. Two glomeruli showing diffuse cellular proliferation and prominence of lobularity. H and E. X 250.

The severity of the disease was recognised by the intensity of cellular proliferation and the percentage of glomeruli having undergone atrophic changes. The electron microscopic examination was carried out on 98 biopsies. The main features were irregular thickening of G.B.M. which contained electron dense deposits in variable situations and an increase in the mesangial matrix along with its cells. The immunofluorescence studies were performed in 88 biopsies. The deposition of IgG and complement C3 was demonstrated along the glomerular loops and mesangium.

Mesangiocapillary G.N. (M.C.G.N.)

(Membranoproliferative G.N)

During the years 1966 and 1980 35 cases of MCGN have been diagnosed. Twenty four of them presented with nephrotic syndrome, associated with heavy proteinuria and haematuria (Table-I and II). Six patients had heavy proteinuria with nephrotic syndrome and five were detected as having asymptomatic proteinuria.

The microscopic examination of this type of nephritis revealed a diffuse intracapillary proliferative changes and conspicuous mesangial widening. There was a fairly uniform mesangial matrix material. The capillaries were narrowed due to widening of mesangial areas and thickening of the basement membrane. The methenamine silver revealed an increased silver positive material in the mesangium which had extended its fibres along the endothelial aspects of basement membrane in such a way that the membrane appeared reduplicated (Fig. 8).

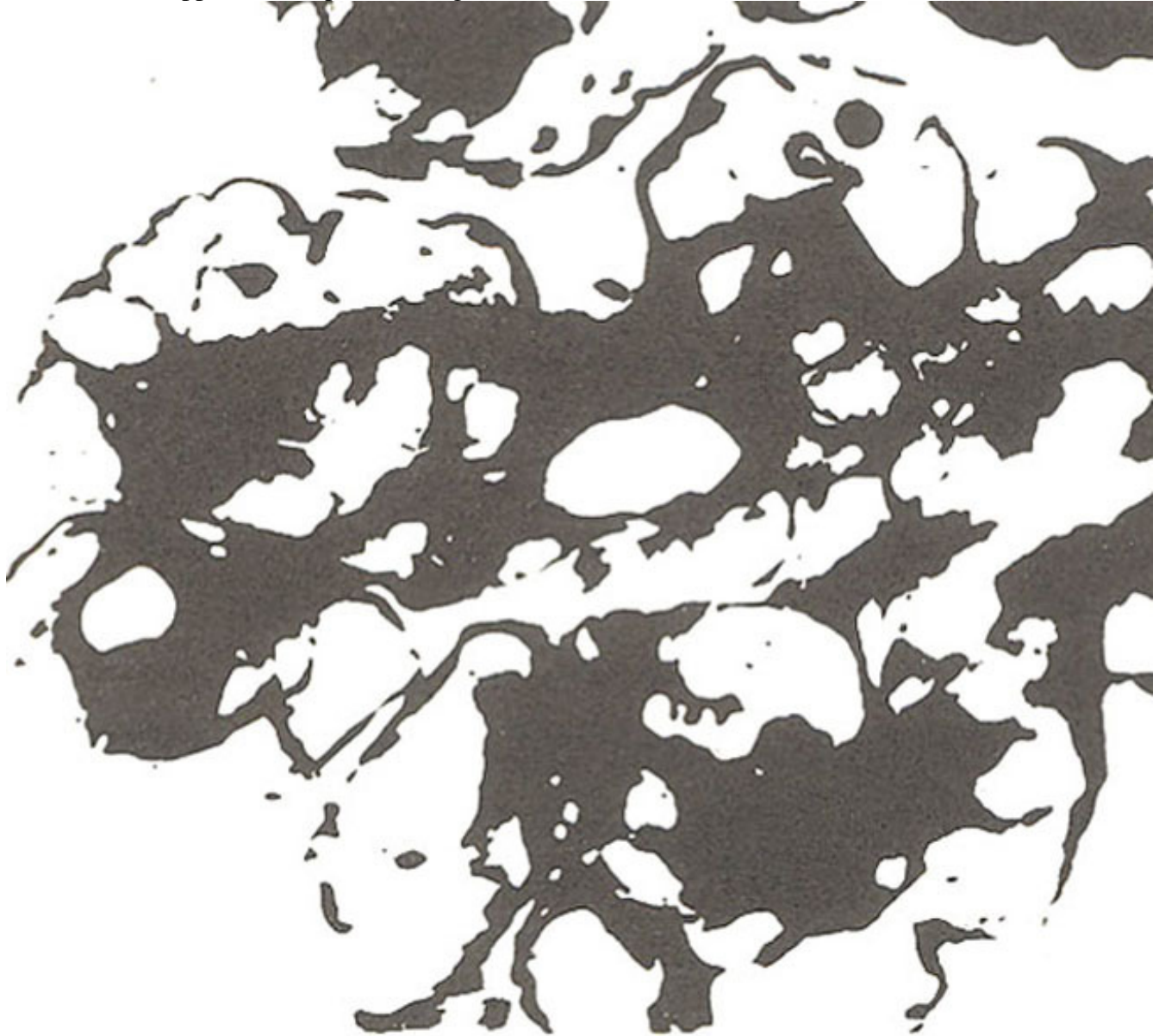


Fig. 8. Glomerular loops showing mesangial widening and G.B.M. reduplication in M.C.G.N., Methenamine Silver X 1400.

The tubules were found to contain rare RBCs and more frequent hyaline casts. By light microscopy, the most characteristic feature was mesangialization of the peripheral capillary loops. The electron microscopy confirmed these findings and showed double basement membrane associated with the

deposition of immune complexes (Fig. 9).

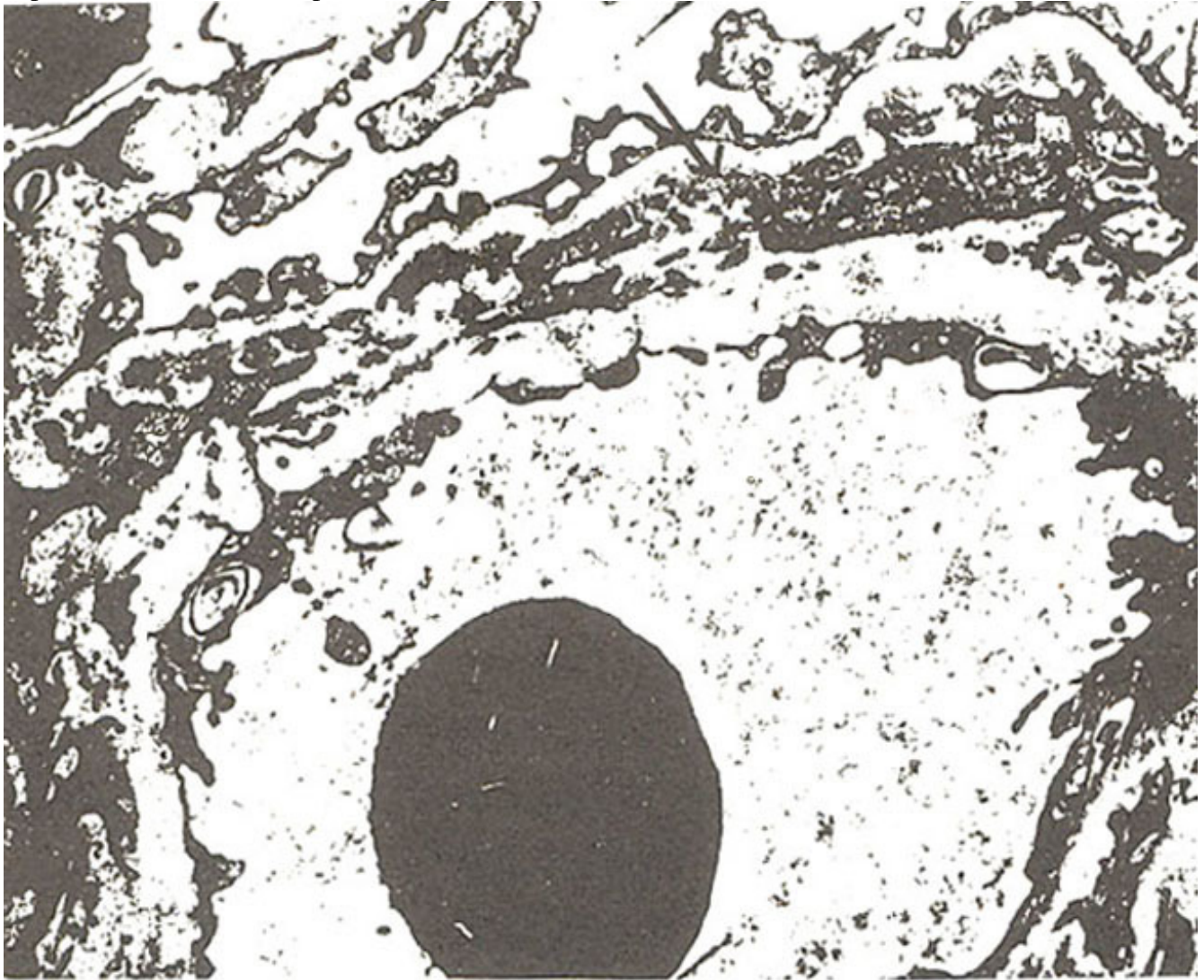


Fig. 9. Electron micrograph of glomerular capillary loop showing double B.M. Note the immune complexes present in it (arrow) X 6000.

The immunofluorescence microscope showed that in 18 of the 35 biopsies irregular deposits of IgG and C3 globulin localised in the capillary loops as well as in the mesangium. Only two of these 15 cases showed IgA, and one biopsy showed the deposition of IgM. The remaining three biopsies showed a linear distribution of the C3 globulin and immunoglobulin IgG. The electron microscopic examination on one biopsy showed continuous deposits within the GBM - the feature of dense deposit disease which is a type of M.C.G.N.

Mesangial proliferative G.N. (Mes. G.N)

All the 16 cases examined presented with nephrotic syndrome (Table-II) associated with proteinuria between 5.2 and 8.5 Gm/24 hours. Two of the 8 cases were moderately hypertensive. Their ASO titres were not raised and their creatinine clearances ranged between 80 ml and 35 ml/minute (Table-II). Microscopically a mild generalized, diffuse proliferation of mesangial cells along with an increase in the

mesangial matrix were observed in all biopsies (Fig. 10).

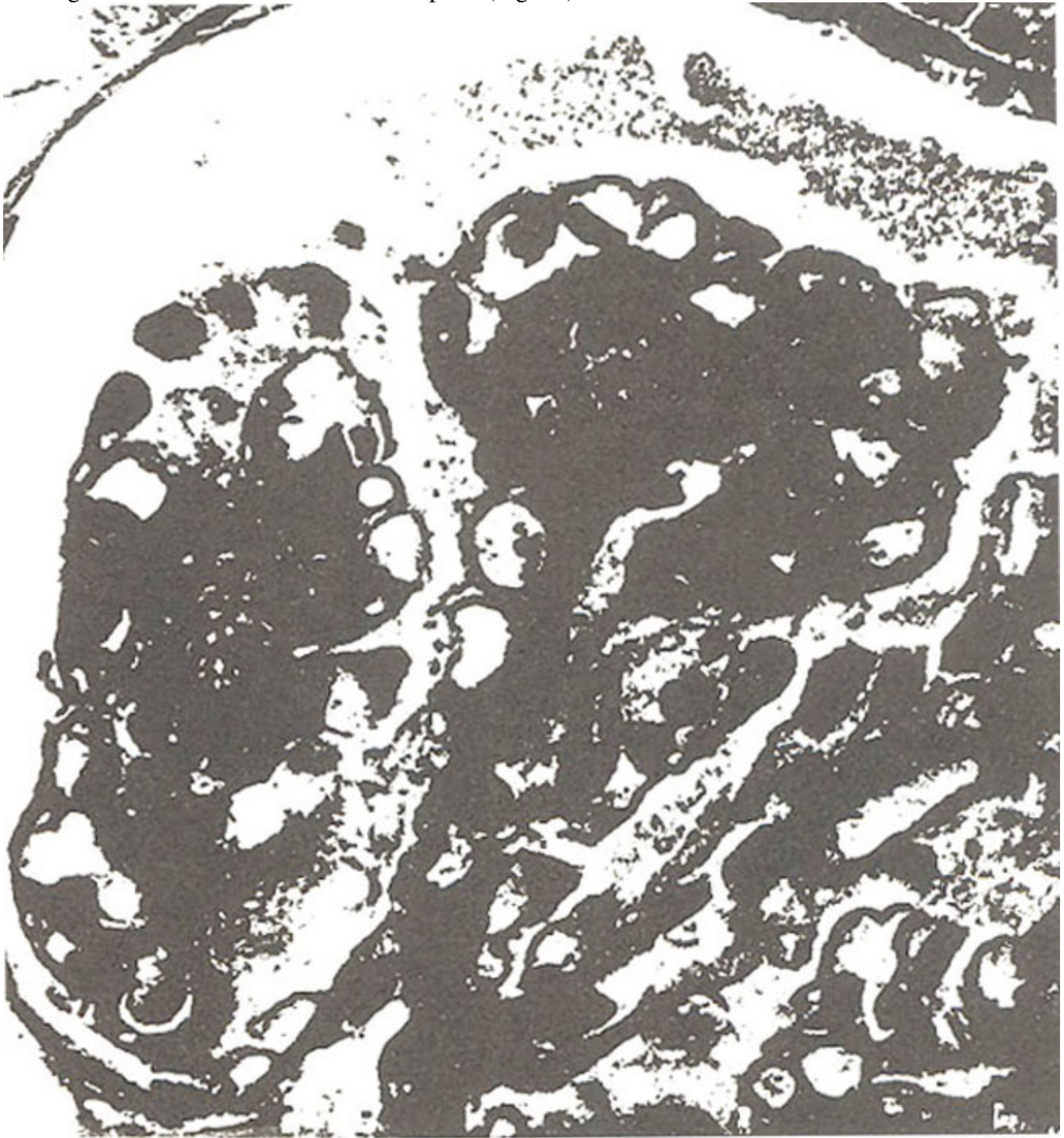


Fig. 10. Portion of a glomerulus showing mesangial cells and matrix having undergone proliferation H and E. X 620.

The capsular epithelial cells were prominent and swollen. Rare glomerular adhesions were observed. The tubulo-interstitial changes included, tubular hyaline casts and mild focal interstitial fibrosis. Deposits of complement and immunoglobulins were present in 3 of 6 cases examined using

immunofluorescence microscope. These deposits in our biopsies occurred mainly in mesangial areas and included variable combinations of IgG, IgM and C3. Electron microscopy was performed only on 5 cases. It confirmed the mesangial cells proliferation, alongwith an increase in the matrix. (Fig.11).

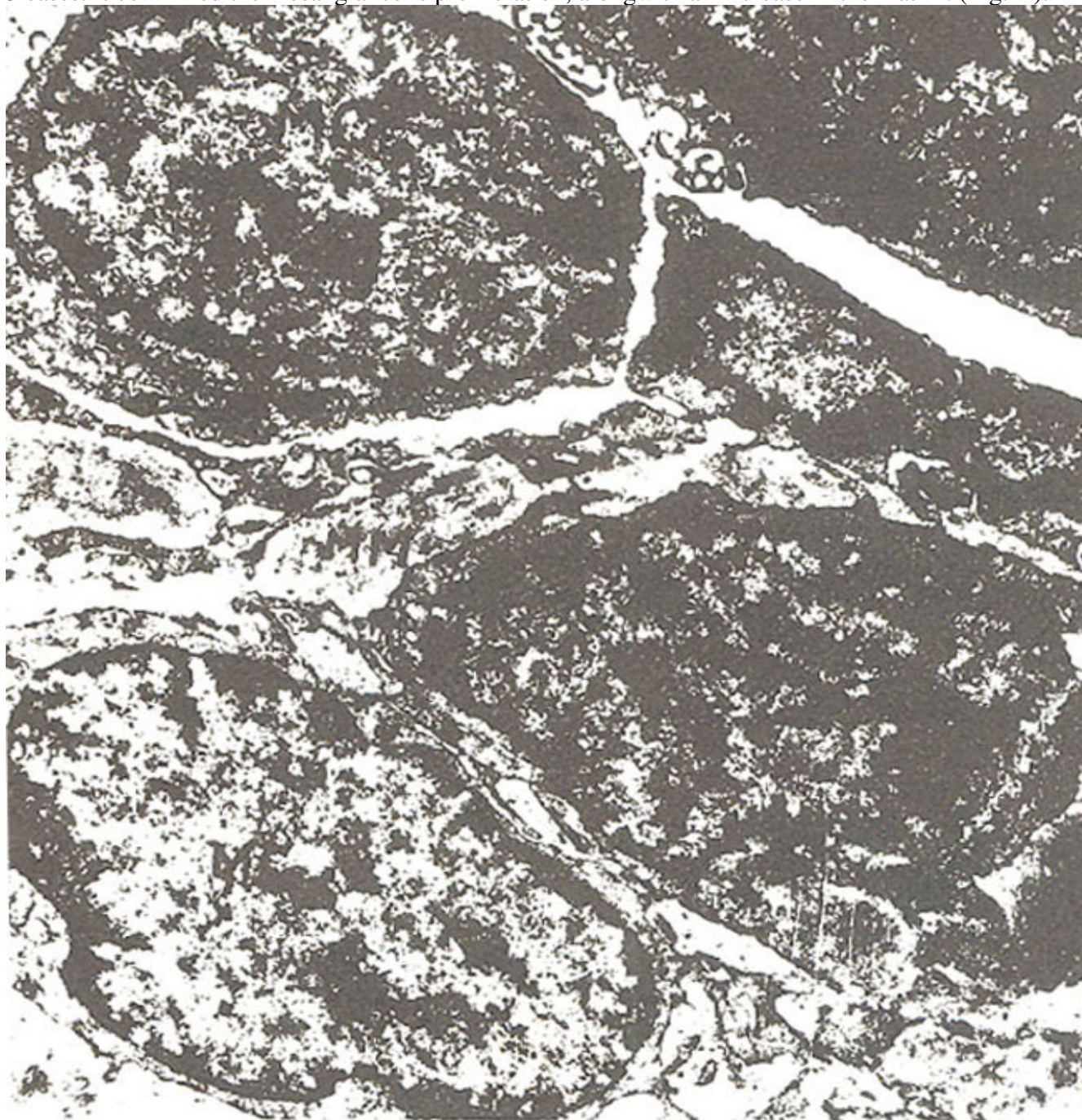


Fig. 11. Electron micrograph showing proliferation of mesangial cells (MC) and increase in electron dense Mesangial matrix (MM) X 9500.

These 5 biopsies showed irregular mesangial deposits. The capillary loops did not show any electron

dense deposits.

Focal glomerulonephritis (F.G.N.)

In a total of 62 cases examined the majority presented with recurrent macroscopic haematuria, nephrotic syndrome or loin pain. Those who had macroscopic haematuria also complained of upper respiratory tract infection. These varied symptoms were associated with mild to moderate proteinuria and microscopic haematuria (Table-I and II). By light microscopic examination several morphological patterns were recognized; 46 of the 62 cases showed focal and segmental lesions consisting of mesangial and endothelial cells proliferation (Fig. 12).

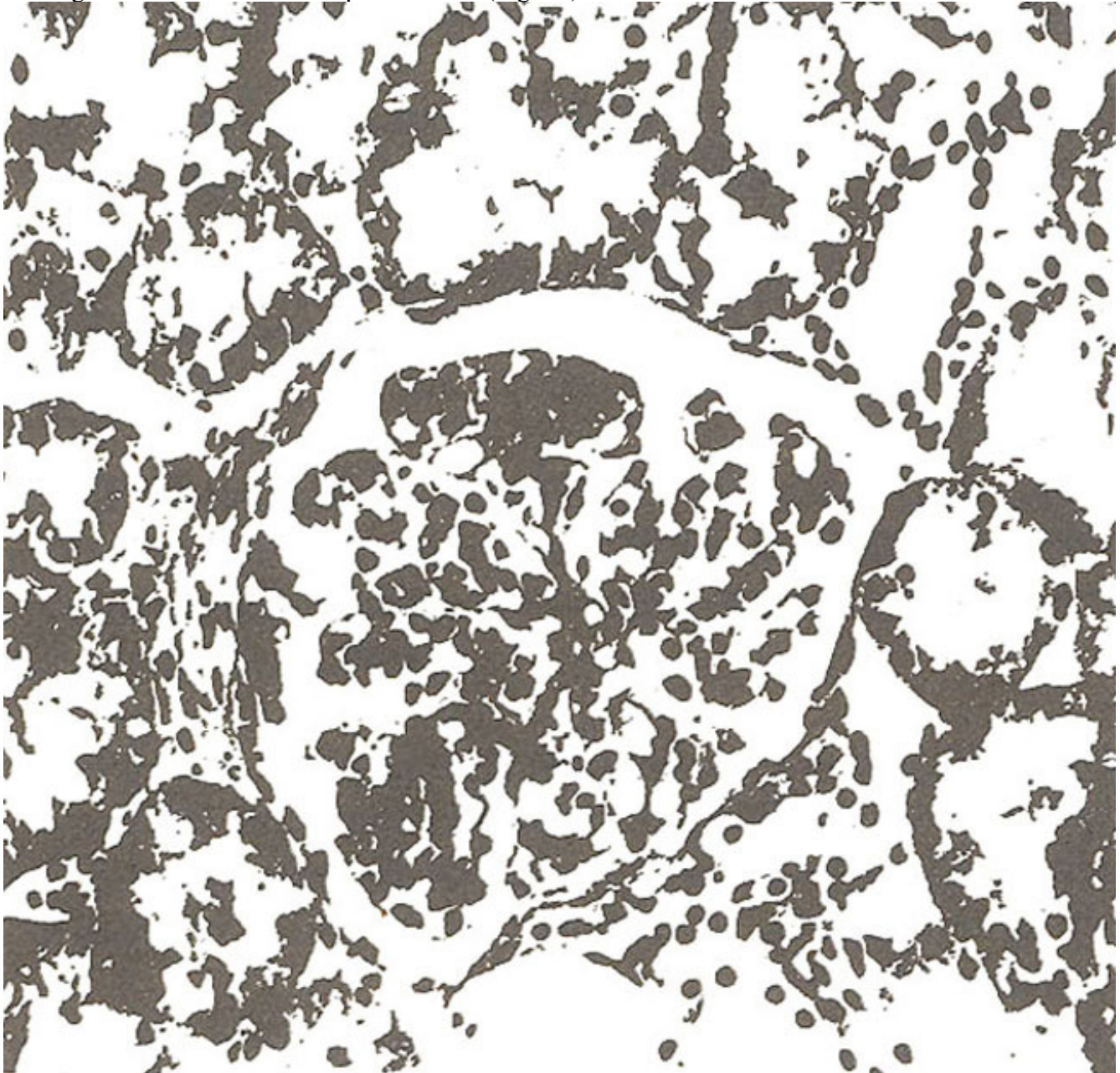


Fig. 12. A glomerulus showing two areas of focal cellular proliferation. H and E. X 250.

The remaining 16 biopsies showed only mesangial cellular proliferation with prominent P.A.S. and silver positive material. In 10 biopsies small focal areas of fibrosis were also found in the vicinity of

cellular proliferative activity. In the majority of cases small areas of tubular atrophy with interstitial fibrosis were seen. The blood vessels however were generally normal. 12 biopsies showed sclerosis of the entire glomerular tuft forming about 25% of the total affected glomeruli.

Immunofluorescent microscopy was performed only on 20 biopsies, 15 of them showed the localisation of IgA, IgG and C3 in the mesangium and sometimes in an occasional peripheral loop. The remaining 5 biopsies did not show deposition of any immunoglobulin or complement. By electron microscopy the glomeruli showed finely granular electron dense deposits in 20 of the 30 cases examined. The remaining cases did not show any obvious electron dense deposits in the glomeruli. Rare deposit was located in the basement membrane of glomerular tuft.

Discussion

As regards the end result of A.P.S.G.N. a large majority is said to undergo healing. The complete healing means no residual hypercellularity and complete reversal of the normal glomerular architecture. On the other hand the term latent GN refers to when evidence of non-healing persists and is a part of continuum which may result in their complete healing, with or without residual structural changes. This latent nephritis or a progressive type of acute GN can pass into a chronic GN (Dodge et al., 1972). In a few cases where acute GN is associated with crescent formation the course of the disease is more rapid and the patient may go into renal failure (Kashgarian et al., 1977). One of our 8 cases who had A.P.S.G.N. showed crescents formation in about 25% of the glomeruli; passed into renal failure and death occurred within a period of 3 months after the diagnosis was made. On the other hand in 4 of the 21 cases of rapidly progressive GN the changes of acute G.N. were noticed whereas the remaining 17 biopsies showed only crescents formation. The cases of extracapillary GN have been immunologically divided into those having linear deposition of immunoglobulin and those where a humpy distribution is observed (Lewis et al., 1971; Sonsino, 1972; Mim, 1974). Both these patterns of deposition were also observed in the biopsies examined on fluorescent microscopy in this series.

Mes. GN formed 3.97% of the 403 biopsies (Fig.1). Its incidence varies between children and adults. In children it forms 6-20% of cases with nephrotic syndrome (White et al., 1970); whereas in adults its incidence is much lower i.e. 1.4 to 9 percent (Cameron, 1968). All the 16 biopsies examined in this series came from adults of 16 to 42 years of age range. In mesangial proliferative glomerulonephritis the clinical onset is variable and may consist of an acute glomerulonephritis episode associated with haematuria, proteinuria or a nephrotic syndrome (Habib and Klein Knecht, 1971). All the cases in the present series presented with clinical nephrotic syndrome; whereas 4 of them had an evidence of macroscopic haematuria and 12 showed microscopic haematuria. In spite of these clinical morphological appearances the overall course and prognosis for a lasting remission is quite favourable (White et al., 1970; Hayslette et al., 1973).

F.G.N. formed 15.39 percent of the biopsies examined (Fig.1). It may be worth pointing out here that all the 62 cases were not associated with any specific systemic disorder such as systemic lupus Erythematosus, bacterial endocarditis, Henoch-Schonlein syndrome, Polyarteritis nodosa and Goodpasture's syndrome. This type of non-specific focal glomerulonephritis has been well documented (Heptinstal and Joekes, 1959 and 1963; McGovern, 1964; Berger, 1968; Rapoport et al., 1970; Nagi, 1973; Meadows, 1978). In addition to its structural pattern, the immunofluorescent studies revealed an immunological nature of this focal G.N. (Nagi, 1973; Roy et al., 1973; McCay et al., 1974; Zimmerman and Burkholder, 1975; Meadow, 1978).

M.C.G.N. formed 8.68% (35 cases) of 403 biopsies analysed. This entity may be recognised by haematuria and proteinuria, nephrotic syndrome or an acute nephritis episode (West, 1973; Habib et al., 1973). Most (71.0%) of the patients presented with the clinical features of nephrotic syndrome with or without haematuria. It is only in 5 of the 35 cases (14.30%) that persistently high levels of ASO titre

were observed indicating that MCGN has some aetiological association with streptococcus. In a series of 36 cases studied by Habib et al. (1975) streptococcus was implicated in 9 (25%). In this characteristic form of glomerulonephritis, variable morphological appearances have been demonstrated (Michael et al., 1969; Nagi, 1972; Zollinger et al., 1973; Habib et al., 1973). Mandalenakis et al. (1971) divided MCGN into lobular and non-lobular forms. Nagi (1972) and Habib et al. (1973) also recognised puremembrano-proliferative and MCGN with lobular pattern. One of the varieties of MCGN has been entitled as Dense Deposit Disease (DDD) which has been well described by various workers (Bariety et al., 1970; Habib et al., 1973; Jenis et al., 1974; Habib et al., 1975; GaHe and Mahieu, 1975). They all described that DDD is a combination of a diffuse cellular proliferation and a diffuse GBM thickening associated with continuous electron dense deposits. As regards the pathogenesis of MCGN, it is considered to be immune in nature (Nagi, 1972; Meadows, 1978). DDD was diagnosed in only one of the 35 biopsies from the cases of MCGN.

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