NEPHROTIC SYNDROME OF ACQUIRED SYPHILIS-A MORPHOLOGICAL AND ULTRASTRUCTURAL STUDY

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Abstract

The histological and electron microscopic structure of eleven cases of nephrotic syndrome due to acquired syphilis is presented. It was observed that in addition to the usual glomerular cell proliferation, the basement membrane showed a variety of changes including different types of electron dense granular deposits. Such ultras-tructural changes suggest an immune pathogenesis responsible for syphilitic nephropathy (JPMA 31:3, 1981).

Introduction

The association between syphilis, both congenital and acquired and nephrotic syndrome is well recognised. In congenital syphilis the renal involvement is usually observed during infancy and early childhood; whereas in the adult form of syphilis it is usually the secondary stage when renal involvement has been observed (Fall et al., 1965; Braunstein et al., 1970; Bhorade et al., 1971). The renal lesions show a marked degree of variation in the involvement of different structures. The objects of the present paper are to demonstrate the variable structural and ultrastructural patterns in nephritis of acquired syphilis. In addition an attempt has-been made to discuss the nature of these lesions and their possible association to the pathogenesis of syphilitic nephritis in adult patients.

Material and Methods

Patients: Eleven patients who came with the history of nephrotic syndrome were included in this study. Their clinical examinations and laboratory investigations were carried out as given under the results. Renal biopsies were performed on all these patients.

Tissue Processing: Each renal biopsy was divided into three portions, the larger two were kept for histopathological and immunofluore-scent examinations; whereas the smaller tissue was further divided into 2-3 blocks for electron microscopy.

Light Microscopy: The tissues for light microscopy were fixed in 10% formolsaline, dehydrated through ascending grades of alcohol,

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cleared in Xylene and impregnated with paraffin wax. The blocks were cut into 4-5 micron thick sections which were stained with haema-toxylene-eosin, periodic acid Schiff reaction, and mcthenamine silver.

Fluorescent Microscopy. The tissue for fluorescent microscopy were cut into 4 micron thick sections using freezing microtome, fixed in 4% phosphate buffered formal saline, pH-7.2 for 2-3 minutes, and stained using antisera to demonstrate immunoglobulins and complement.

Electron Microscopy. Small blocks of renal biopsy were fixed in 1% Osmic acid dehydrated in grades of ethanol and embedded in Epon. Ultra-thin sections stained with urenyl acetate and lead citrate were examined on an EM GB electron microscope.

Results

Clinical Features:
All the eleven patients were adult males and presented with the clinical features of nephrotic syndrome. Six of them reported with moderate to severe generalised oedema and ascites. The remaining five patients had puffi-ness of face and periorbital oedema. All of them gave a past history of contact, whereas only eight volunteered the formation of primary chancre involving the penis or scrotum. Most of these patients received irregular therapy and local applications on chancre by quacks (Table-I).

Table I: Clinical Features and Therapy

Case No.	Age/ Sex	OEDEMA			HAEMATURIA		B.P. in mmHg	Duration since contact	History of chancre formation	THERAPY IN WEEKS		
		Face	Ankle	Generalised	Micro	Macro				Local	Systemic	Nature
1.	26/M	—	—	+++	—+	+	140/85	5 months	Yes	2	None	Not known
2.	36/M	—	—	+++	++	—	140/80	8 months	Yes	1	,,	—Do—
3.	25/M	—	—	++	—	—	130/80	6 months	Yes	1	,,	—Do—
4.	32/M	++	—	—	—	—	140/85	9 months	Yes	None	,,	—Do—
5.	46/M	++	+	—	—	—	160/90	14 months	No	None	1 week	Erythromycin
6.	40/M	++	+	—	+	—	152/90	12 months	No	None	1½ week	—Do—
7.	35/M	—	—	++	—	+	145/85	8 months	Yes	1	1 week	—Do—
8.	34/M	+	++	—	—	—	130/80	14 months	Yes	2	None	Not Known
9.	38/M	—	—	+++	—	+	140/80	12 months	Yes	3	None	—Do—
10.	35/M	++	+	—	—	—	148/82	10 months	Yes	1½	None	—Do—
11.	40/M	—	—	+++	—	—	158/92	15 months	No	None	None	—Do—

0 to ++++ = ARBITRARY GRADING OF SEVERITY.

Laboratory Investigations

Table II: Biochemical and Serological Investigations

Case No.	Urinary Protein per 24 Hr.	Total Serum Protein g%	Serum Albumin Globulin g%	Creatinine clearance ml/min.	Blood Urea mg%	Serum Cholesterol g%	W.R.	VDRL	Kahn's Test	F.T.A.	T.P.I.
1.	8.2	4.9	2.5/2.4	70	56	300	+VE	VE	+VE	++VE	+VE
2.	4.8	6.2	3.0/3.2	118	38	298	+VE	+VE	+VE	Not Performed.	Not Performed.
3.	6.0	4.8	3.0/2.8	72	42	305	+VE	+VE	+VE	,,	,,
4.	7.2	5.2	3.1/2.1	62	60	360	+VE	+VE	+VE	,,	,,
5.	10.2	4.6	2.5/2.1	52	70	372	+VE	+VE	+VE	++VE	+VE
6.	5.9	6.0	3.2/2.8	80	52	310	+VE	+VE	+VE	Not Performed.	Not Performed.
7.	10.0	5.0	3.0/2.0	58	72	352	+VE	+VE	+VE	,,	,,
8.	9.1	5.5	3.1/2.4	60	40	325	+VE	+VE	+VE	++VE	+VE
9.	8.5	8.9	3.4/2.5	71	68	302	+VE	+VE	+VE	++VE	+VE
10.	6.2	6.2	3.1/3.1	78	60	299	+VE	+VE	+VE	++VE	+VE
11.	5.5	6.0	3.0/3.0	92	45	300	+VE	+VE	+VE	+VE	+VE

+VE=Positive 0++++ = Arbitrary intensity of Fluorescence.

Table II shows the details of biochemical and serological findings in all the eleven cases.However, urinary protein excretion of 4.8 per 24 hours to 10.2 g per 24 hours was observed. The total serum proteins ranged between 4.6 g per cent to 6.2 g per cent and serum electrophoresis showed a fall in albumin and rise in gamma globulin levels. The serum cholesterol rose to a range of 298 mg to 372 mg per cent. Serum urea was between 38 mg per cent and 72 mg per cent; whereas creatinine clearance ranged between 8 ml/minute and 52 ml/minute. The serological investigations for syphilis included VDRL, Wassermanns Reaction, Kahn's test and on six patients fluorescent treponemal antibody absorption and TPI tests for syphilis.

Light Microscopy

Most glomeruli were prominent by mesan-gial and endothelial cellular proliferation, and showed capsular adhesions (Fig. I).

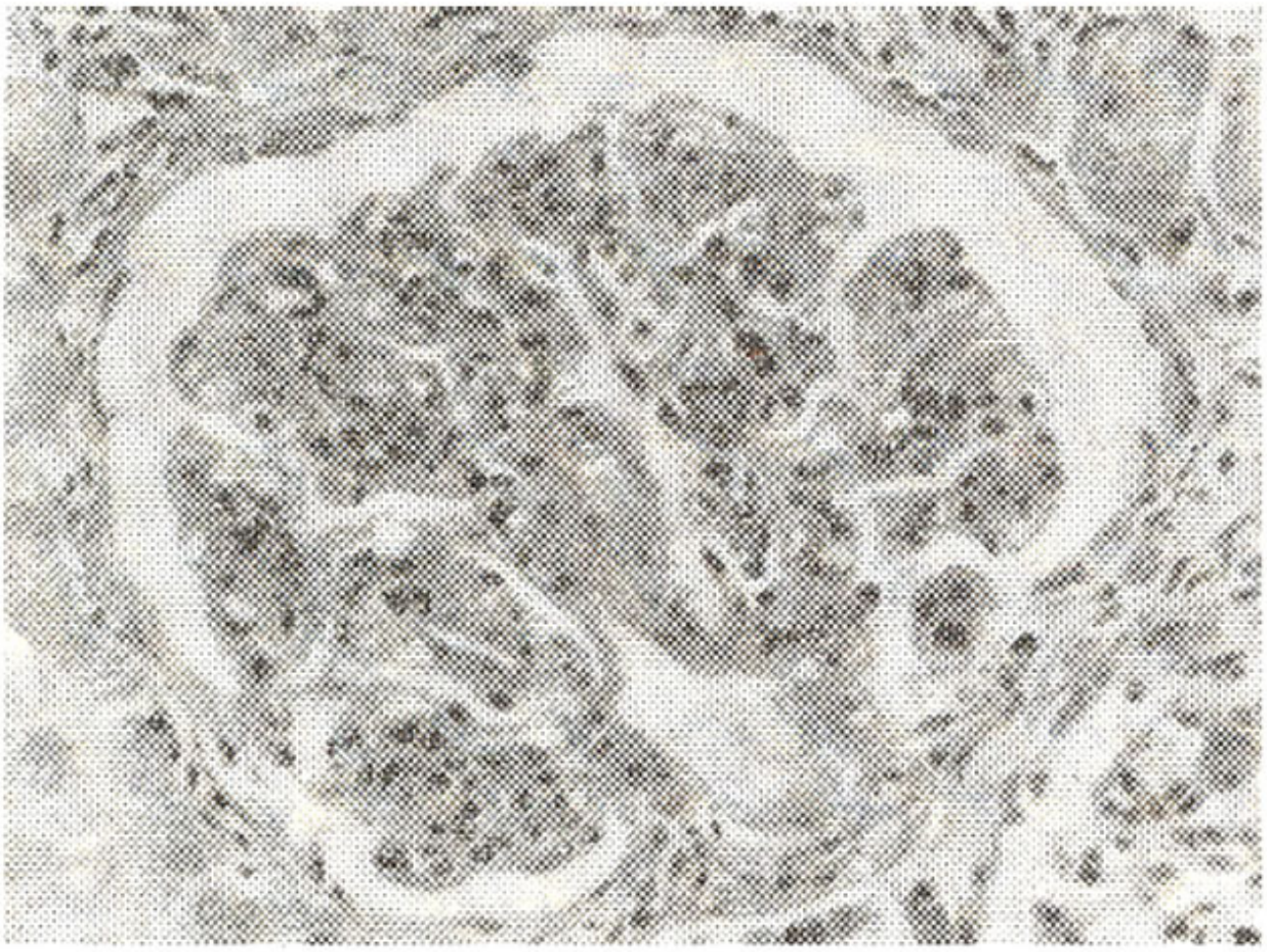

Fig. 1. A glomerulus showing a diffuse mesangial and endothelial cell proliferation. An area of capsular adhesion (arrow) is also seen. Haematoxyline and eosin x 450.

In other biopsies epithelial crescent was a prominent feature (Fig. 2).

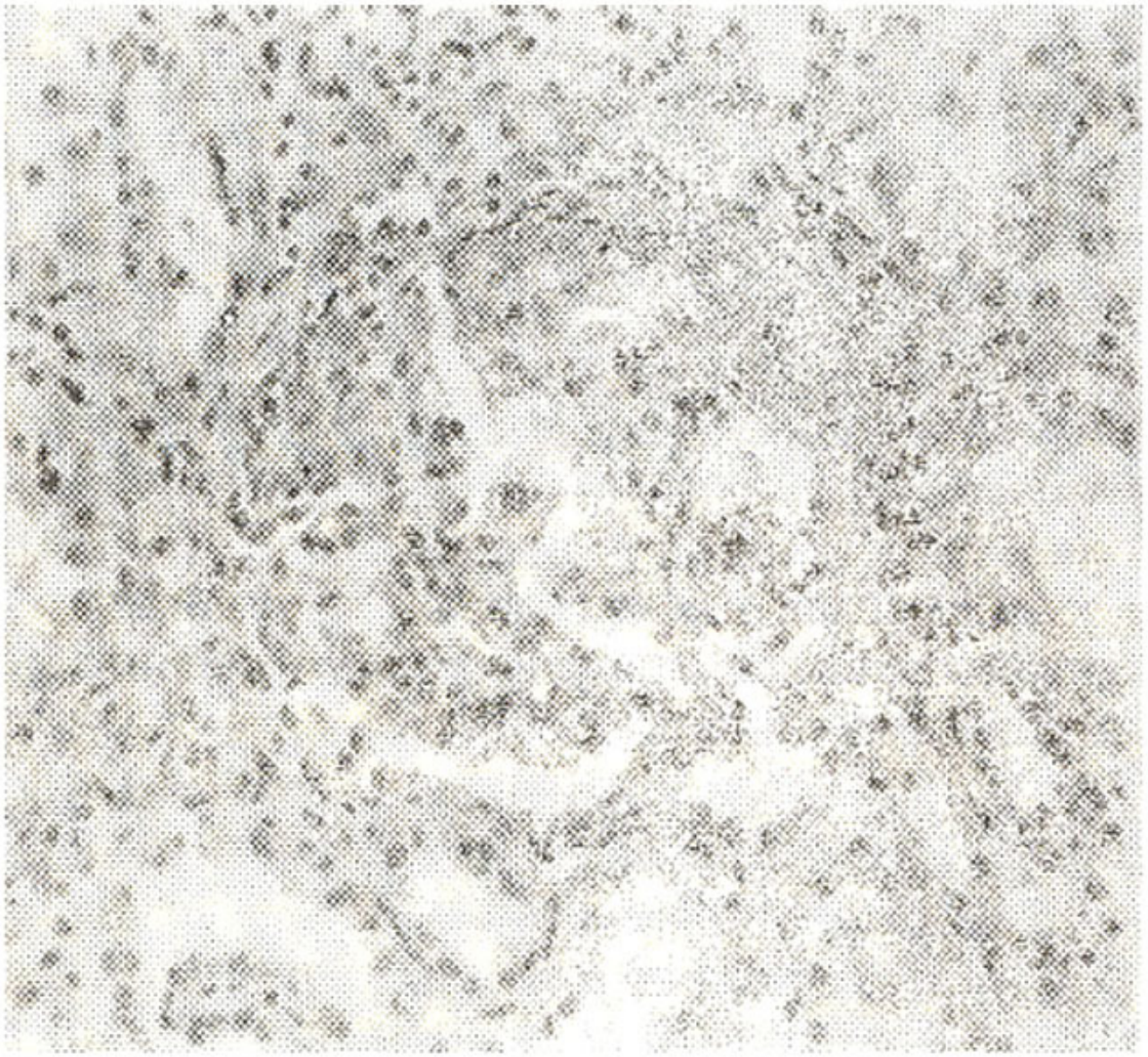

Fig. 2. Glomerulus showing epithelial proliferation and crescent formation. Haematoxyline and eosin x 380.

A mixture of such cellular pro-liferation was also a frequent finding. A common feature in all the biopsies was thickening of the glomerular basement membrane (GBM) which showed irregularly distributed methenamine-silver positive projections (Fig. 3).

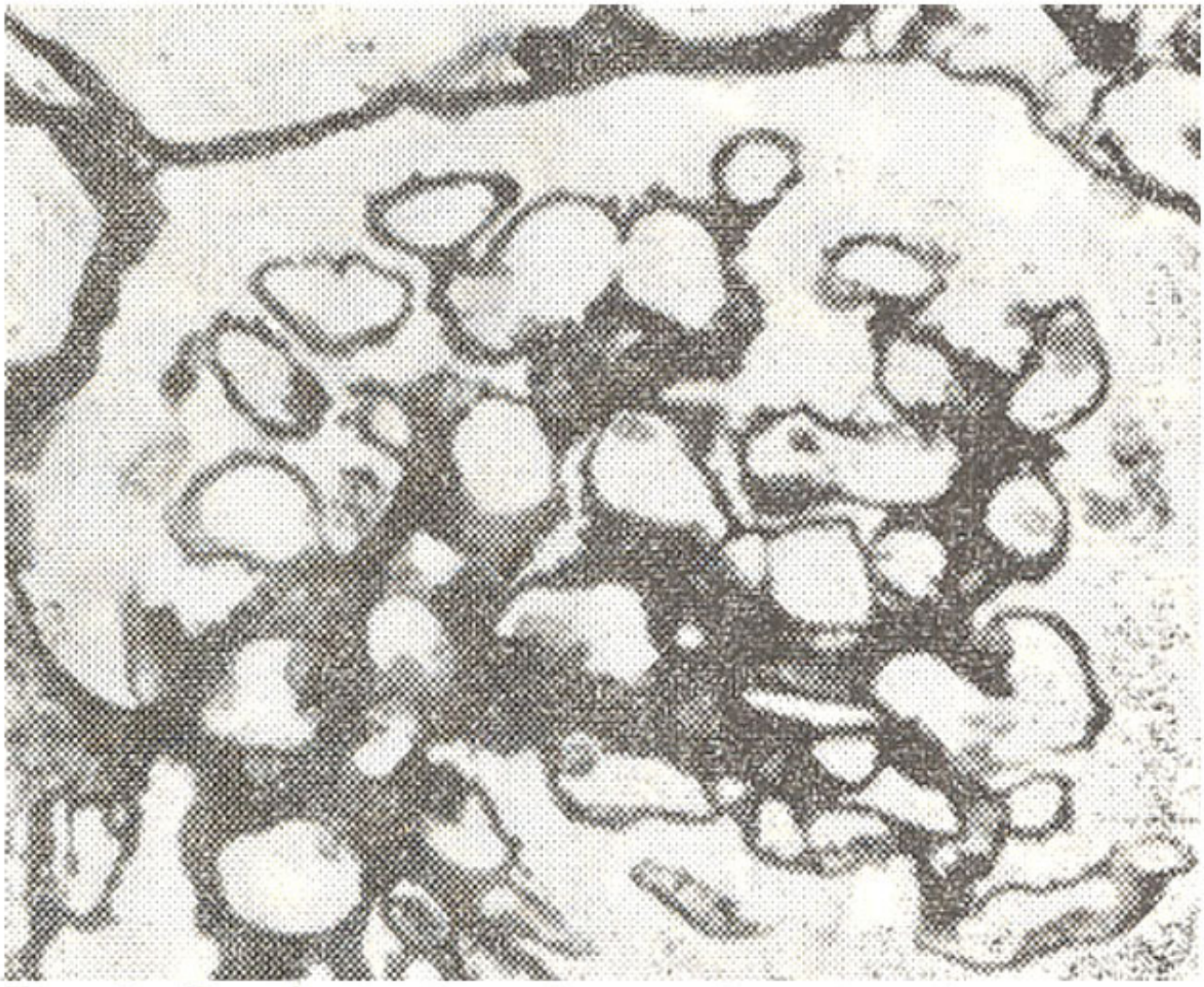

Fig. 3. Portion of a glomerulus showing methenamine silver positive epithelial projections. Methenamine silver x 940.

In addition, an increase in the mesangial tissue was observed in most of the biopsies. In long standing cases the tubules showed various stages of atrophy and dilatation. The blood vessels at all levels did not show any remarkable change. The interstitial tissue in most of the biopsies showed moderate infiltration by lymphocytes and plasma cells (Fig. 4).

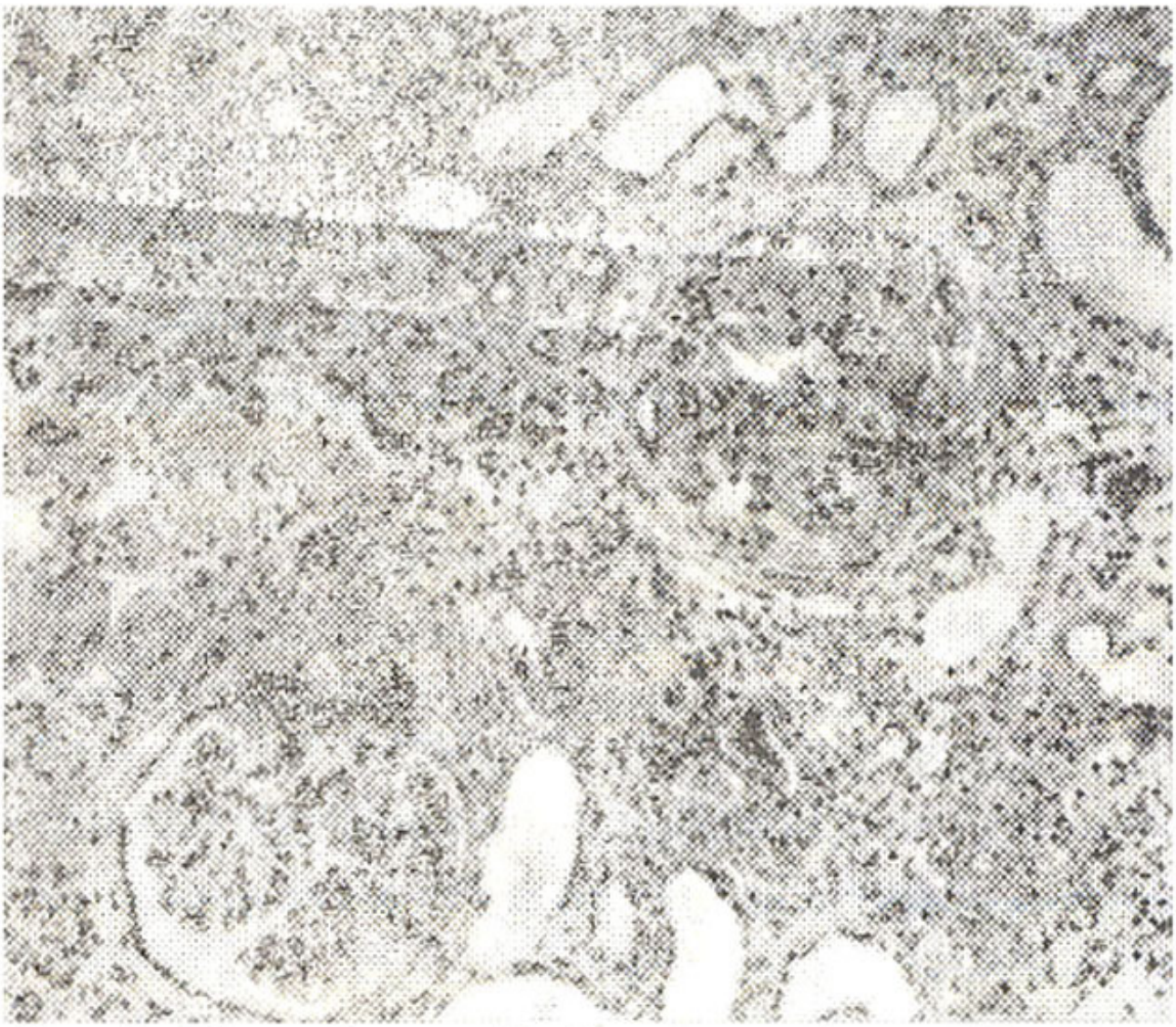

Fig. 4. Two glomeruli showing cel proliferation and capsular adhesions. The stroma shows lymphocytic and plasma cell infiltrate. Haematoxyline and eosin x 250.

Fluorescent Microscopy

Immunofluorescent studies could be performed only on four biopsies. In most of the biopsies the fluorescent staining tended to be patchy and it was most obvious with anti-IgG and anti-complement, whereas anti - IgM, anti-fibringen serum produced no reaction. One of the four biopsies showed a distribution of IgG indistinguishable from membranous nephropathy (Fig. 5).

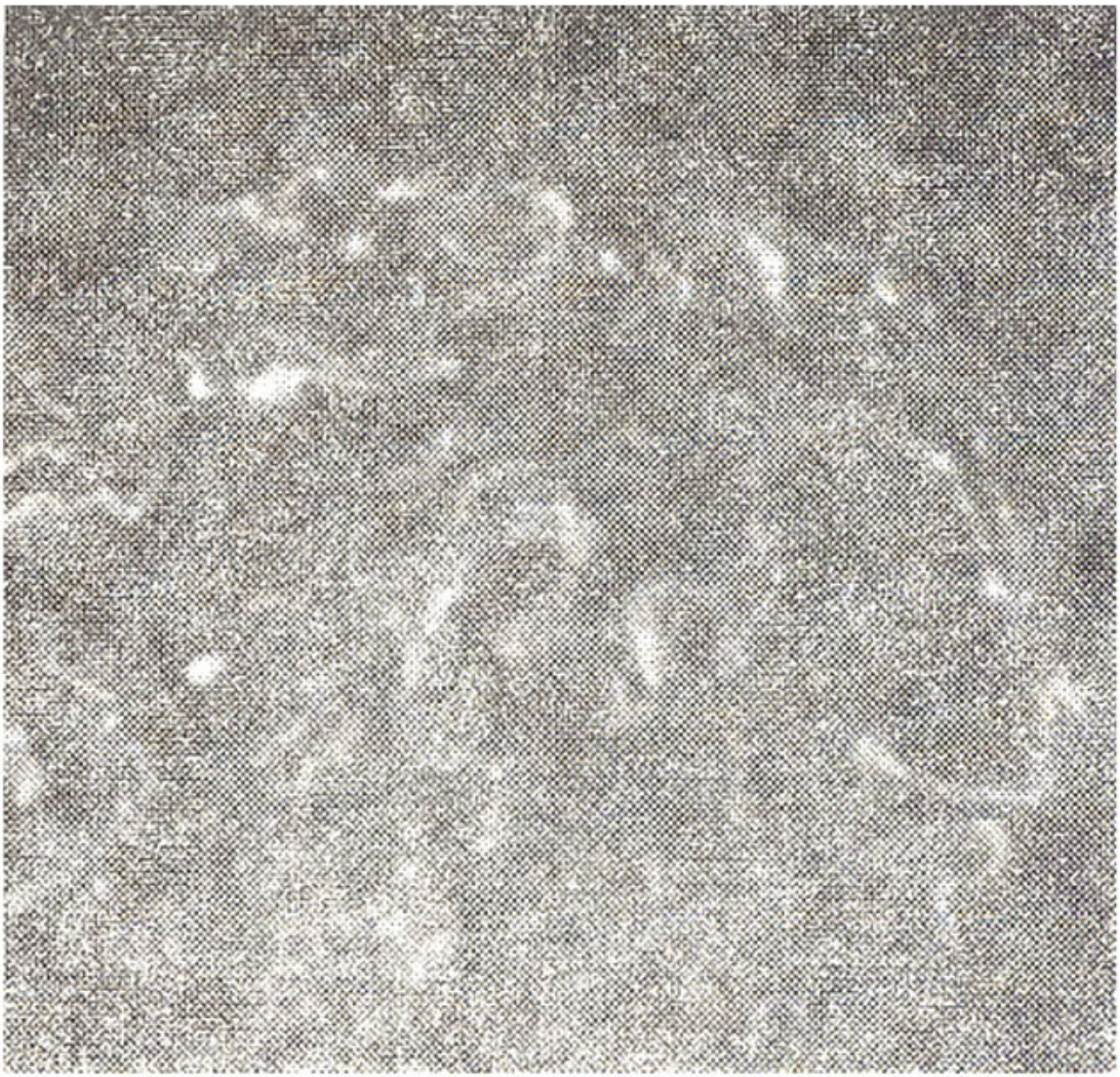

Fig. 5. Portion of glomerulus showing deposition of immunoglobulin IgG along the capillary basement membrane x 980.

Electron Microscopy

The electron microscopic changes, like histological appearances, varied from one glomerulus to another. Electron dense osmiophilic deposits were found in various situations on the basement membrane. Three of the 11 biopsies showed a frequent presence of such deposits along the epithelial aspect of GBM (Fig. 6)

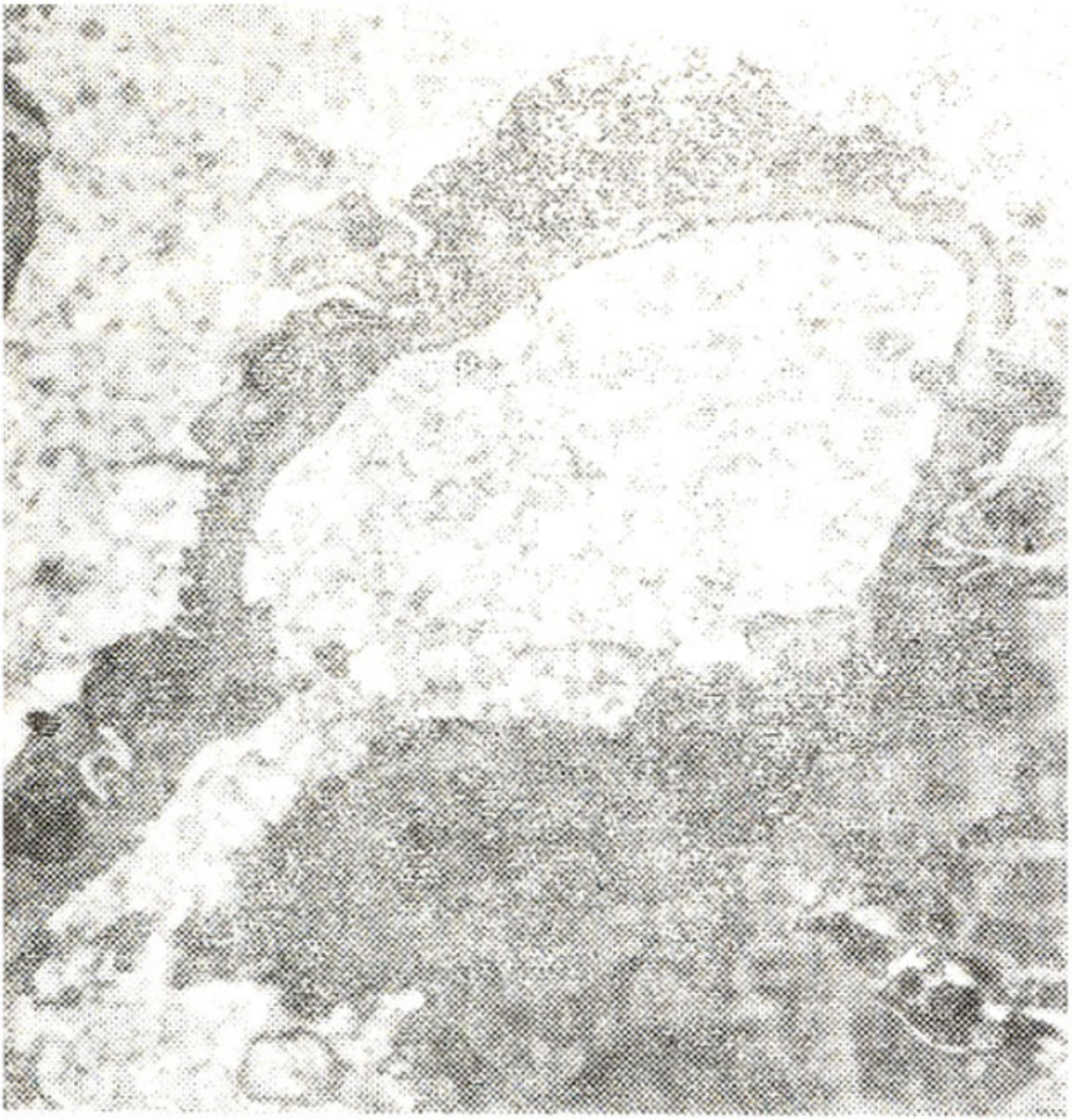

Fig. 6. An electron micrograph of a glomerular loop showing mumeous osmiophilic electron dense deposits along the epithelial aspect of basement membrane x 6400.

with fusion or loss of epithelial foot processes overlying these electron densities. In four cases the deposits were seen within GBM replacing the lamina densa in the affected loops |(Fig. 7).

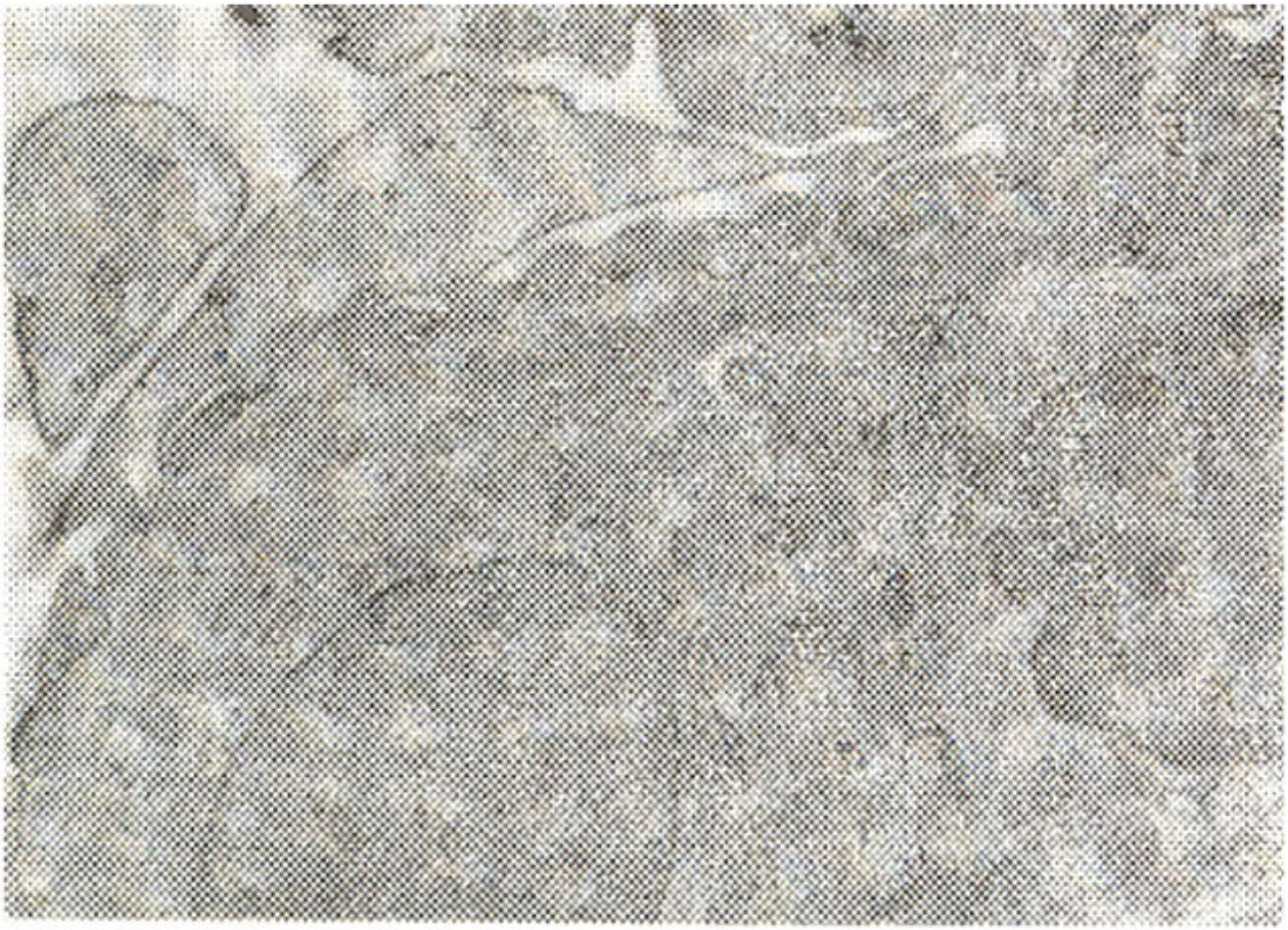

Fig. 7. Electron micrograph of a glomerular loop showing intramembranous osmiophilic deposits x 8200.

Some of these intramembranous deposits were seen in the various stages of regression which is indicated by the appearance of light areas around and some times within the deposits giving them a micro-honeycoomb pattern (Fig. 8).

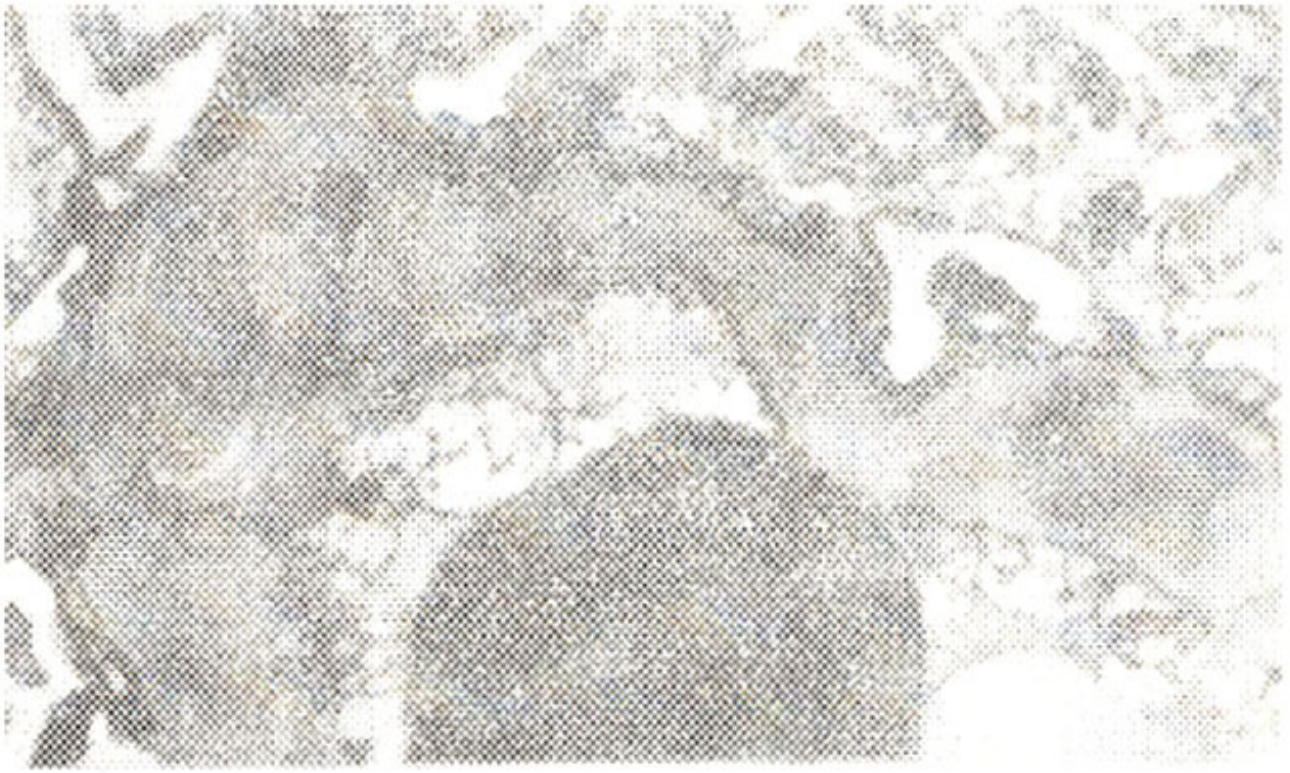

Fig. 8. Portion of a glomerular loop showing various stages of regression of the electron dense deposits with clear areas around them (arrow) x 14300.

The four remaining biopsies contained the deposits having coarse granularity (Fig. 9)

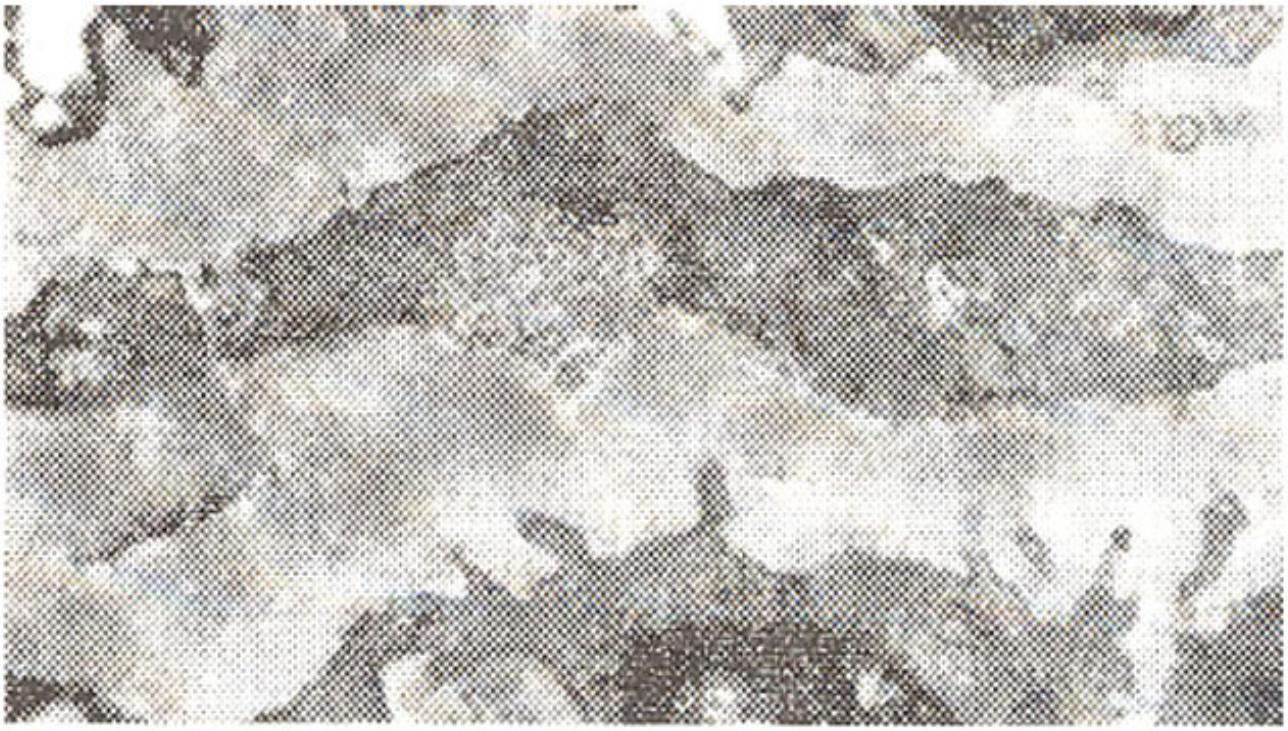

Fig. 9. Electron micrograph of a glomerular basement membrane showing a coarsly granular subepithelial deposits x 15600.

or multivesicular appearance (Fig. 10).

Fig. 10. Portion of a glomerular loop showing multivesicular electron dense deposits towards endothelial aspect of a thickened basement membrane x 15600.

They were situated either within the GBM expanding it towards the luminal aspect or present along its epithelial aspect. Some times similar isolated granules or vesicles have also been observed along the subepithelial margin. In one biopsy membrane irregularities were observed both along its epithelial and endothelial aspects. They were caused by the presence of electron dense deposits of fine granularity

(Fig. 11).

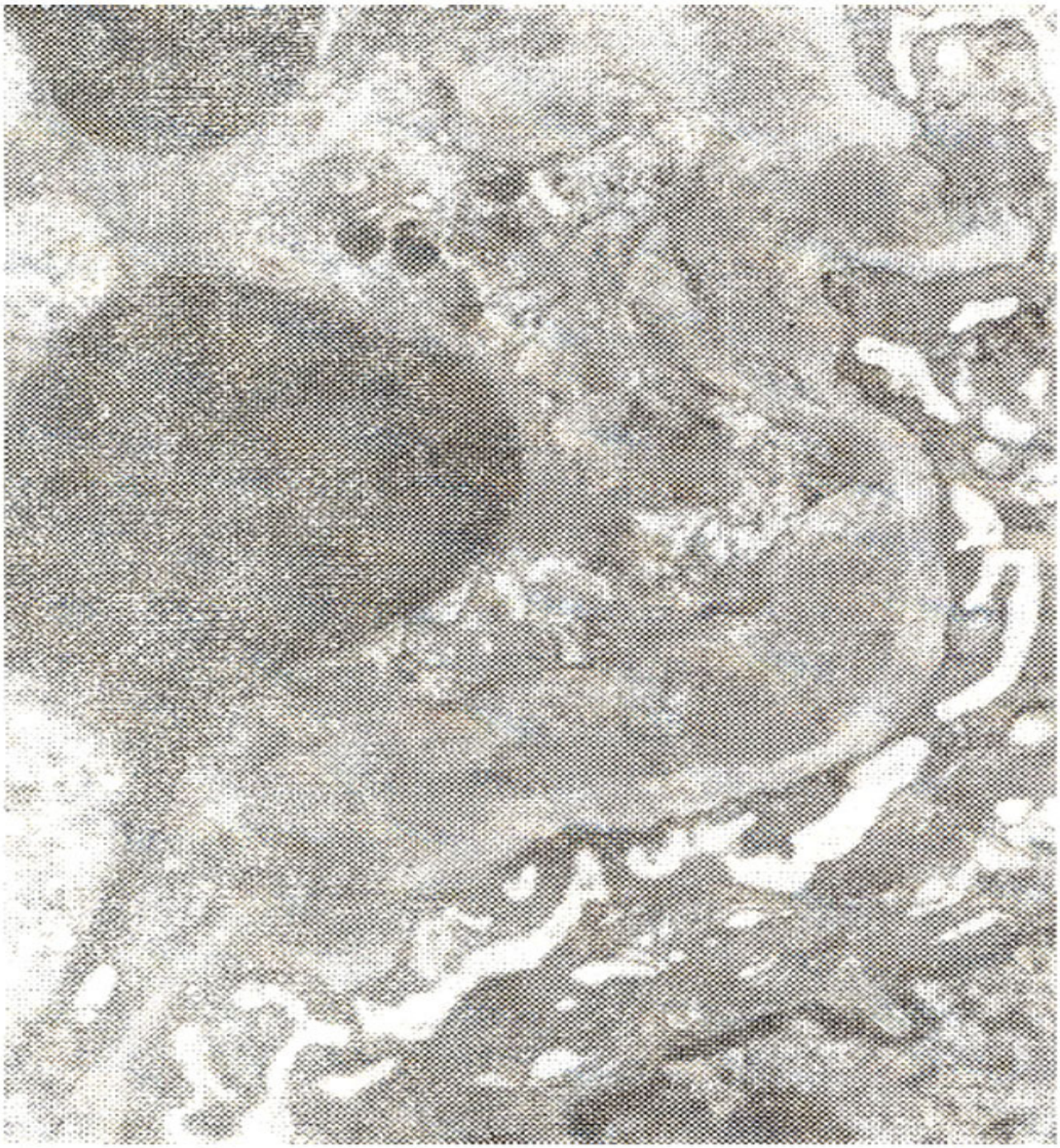

Fig. 11. Portion of a glomerular loop showing a combination of subendothelial and subepithelial osmiophilic deposits (arrow) x 7600.

The tubules and the blood vessels did not show any remarkable change specific of syphilitic nephritis.

Discussion

The usual histological appearance in the kidney of syphilis is interstitial infiltration by lymphocytes and plasma cells. The picture is not usually regarded responsible for the clinical manifestations of nephrotic syndrome. Such clinical appearances are associated with glomerular changes manifested in the form of cellular proliferation and irregular thickening of the basement membrane (Fall et al., 1965; Hill et al., 1972; Yuceoglu et al., 1974). Similarly, the changes seen in our cases were, glomerular enlargement with mesangial and epithelial cellular proliferation. The GBM was found to be irregularly thickened with methenamine silver positive epithelial projections. In some cases epithelial cell proliferation was a prominent feature.

The electron microscopic appearances described so far are all indicative of the presence of immune complexes, seen as osmiophilic electron dense deposits (Braunstein et al., 1970; Mc Cluskey, 1970; Bhorade et al., 1971; Kas-chula et al., 1974).

In the present group of patients in addition to the confirmation of cellular proliferation and an increase in the mesangial matrix, the irregularity of the GBM was found to be mainly due to electron dense deposits of variable appearance.

These deposits were situated at all sites in the GBM, including subepithelial, intramembranous and subendothelial areas. The most common situations for these deposits in the present study were intramembranous and subepithelial aspects of the GBM, whereas the mixed variety was observed in only one biopsy.

As regards the pathogenesis we believe that the presence of electron dense deposits and gamma globulins are suggestive of an immune complex mechanism. Braunstein et al (1970) in his report of the structural changes and flourescent studies in syphilitic nephritis failed to demonstrate treponemal antigen. What is the nature of antigen and the exact events which lead to the glomerular damage is however not known.

Lastly it will be worth considering that the nephrotic syndrome of acquired and congenital syphilis may not be as uncommon, as it is believed. Moreover, it should be strongly suspected in individuals who give history of contact followed by clinical evidence of syphilis, and remained under treated or untreated for this condition. The importance of diagnosing this f condition lies in the fact that type of immune complex disease it causes can be reversed by using penicillin (Yuceoglu et al., 1974).

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