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Electron Microscopy of Nephropathia Epidemica

Glomerular Changes

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Summary. Electron microscopical changes in the glomeruli in 20 kidney biopsies from 18 patients, who were suffering from or had lately suffered from Nephropathia epidemica were studied. Various kinds of deposits were seen. Under the endothelial cells there were collections of light flocculent material. Small dark deposits were seen in the mesangium at the mesangial cell processes, inside the thickened basement membrane, and occasionally on the epithelial side of the membrane. Large deposits were seen around mesangial cells in the mesangium. Deposits were less numerous than in chronic immune complex diseases. The intramembranous or subepithelial deposits were associated with "moon craters", membranous convoluted structures or membrane debris. Granular extracellular mesangial material, round extracellular particles and intraendothelial microtubular inclusions were occasionally seen. In two of our cases occasional capsular epithelial cells showed numerous myelin bodies. Typical viruses were not seen in the glomeruli. The findings are in accord with the short period of scanty immune complex deposition in the glomeruli in the clinically active phase of Nephropathia epidemica.

Key words: Nephropathia epidemica – Hemorrhagic fever – Glomerular changes – Immune complex disease – Electron microscopy.

Introduction

In 1934 Zetterholm and Myhrman independently described a disease occurring in north-central Sweden. This disease was characterized by an acute onset with high fever followed by abdominal pains, and a renal syndrome with heavy proteinuria and oliguria (Lähdevirta, 1971). Myhrman (1945) recommended the name "Nephropathia epidemica" for this disease. The disease has since been found in Scandinavian countries (Stuhlfauth, 1943; Hortling, 1946; Hansen,

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1958; Ornstein and Söderhjelm, 1965; Lähdevirta, 1971; Mouland, 1975; Lähdevirta and Elo, 1975; Nyström, 1977) and about 2500 cases have been reported. The similarity of this disease with the hemorrhagic fever with renal syndrome which occurs in the U.S.S.R. (Gajdusek, 1953) and central and southeastern Europe (Trencséni et al., 1955; Trencséni and Keleti, 1971), and with the epidemic hemorrhagic fever described during the Korean war (Gajdusek, 1962) is notable. The etiology is unknown, but is probably viral. Histological investigation shows hemorrhagic interstitial nephritis, changes being mostly localized in the medulla (Kuhlbäck et al., 1964). Glomerular changes are also found (Lähdevirta, 1971) and immunohistochemical studies (Jokinen et al., 1977) have shown immune complex glomerulitis. This study aims at an ultrastructural description of the glomerular changes in this disease.

Patients and Methods

The material consists of 20 biopsies from 18 patients taken during and after the acute phase of the disease. The earliest sample was taken 3 days and the latest 7.5 months after the onset of fever. Two patients were biopsied twice. The patients and their clinical findings are presented in Table 1. Diagnosis was based on typical clinical symptoms and signs of the disease (Lähdevirta,

Table 1. The material of 18 NE patients with 20 renal biopsies ordered according to the time of biopsy after onset of fever. The day of onset of fever is counted as the first day

The time of renal biopsy after onset of fever	Patients: Sex Age, years	Peak value of serum creatinine µmol/l	Peak value of urine protein per mille	Peak value of urinary output during polyuric phase ml/day
3rd day	♀, 38	270	2	3000
6th day	♂, 21	700	11	5800
6th day	♂, 25	112	0.5	3000
9th day	♂, 22	531	5	4800
9th day	♂, 34	670	12	4600
10th day	♂, 15	468	2	3000
13th day	♂, 36	354	6.5	6000
13th day	♂, 47	689	12	6000
13th day	♀, 56	707	1.5	3700
14th day	♂, 31	265	9	3650
14th day	♂, 28	115	1	4550
18th day	♂, 63	248	5.5	3200
19th day	♂, 19	207	2	2700
20th day	♀, 17	453	2	3400
25th day	♂, 24	705	3	3700
25th day	♀, 54	274	4	3400
28th day	♂, 62	212	3	3650
35th day	♂, 39	910	16	9000
3.5 months	♂, 39	910	16	9000
6.5 months	♂, 47	689	12	6000

Together 20 biopsies from 18 patients of which 4 females, and 14 males, with a mean age 35.1 years (range from 15 to 63 years). There were 4 mild (serum creatinine less than 250 µm/l), 13 moderate (serum creatinine between 250 and 900 µm/l), and 1 severe (needed hemodialysis) case

1971). The biopsies were taken with a Silverman needle (Goldman's modification). The tissue fragments were placed in chilled Ringer's solution and divided into three portions, one of these for electron microscopy.

The latter was fixed in 3% phosphate-buffered glutaraldehyde (pH 7.3) for 3 h, transferred into 0.2 molar phosphate buffered sucrose solution and kept there for 1–6 days at +4° C. After this the piece was postfixed in 1% phosphate-buffered osmium tetroxide, for 1 h, dehydrated and embedded in Epon. Ultrathin sections were cut with glass knives and stained with 1% uranyl acetate in 50% ethanol and with lead citrate. Semithin 1 μm thick sections were also cut and stained with 1% methylene blue in 1% sodium borate solution. Electron microscope sections were studied with a Hitachi HS 7S electron microscope.

Results

Light Microscopy

There were 1 μm thick Epon-embedded, methylene blue stained sections of all cases available. In addition, of ten patients paraffin sections stained with H&E, van Gieson, PAS and trichrome stains were studied. The interstitial findings varied greatly depending on the site of the biopsy in the kidney and on the stage and severity of the disease. In some cases only slight interstitial oedema was seen whereas in other cases there was inflammatory infiltrate and in later samples fibrosis. In biopsies of the medullary areas there was extravasation of red blood cells, oedema and an inflammatory infiltrate consisting of lymphocytes, macrophages, fibroblasts, plasma cells and occasional mast cells and granulocytes. Increased cellularity in the glomeruli was seen in a few early samples but also in the biopsy taken 35 days after the onset of fever. Changes in the glomerular basement membrane (thickening, mesangial prominence) was seen in biopsies taken later than 10 days after the onset of fever. Occasionally hyalinised glomeruli could be seen. Thickening of the capsular basement membrane and periglomerular fibrosis was seen in a few cases. The light microscopic findings were similar to those reported by Lähdevirta (1971).

Electron Microscopy

The glomerular basement membrane (GBM) was thickened at the mesangial areas but in occasional glomeruli also around the peripheral capillaries (Fig. 1). There was increase in the mesangial matrix material at places (Fig. 2). The GMB often appeared to be thrown into folds at the mesangial areas (Figs. 1, 2).

In the minority of samples there were signs of endothelial or mesangial cell proliferation. Granulocytes or cells with large cytosomes suggesting phagocytic activity were found in a few cases (Fig. 3). In places the epithelial cells were bulky and filled all the space between capillary loops. Fusion (retraction) of the foot processes was common at the mesangium but not at the peripheral GBM.

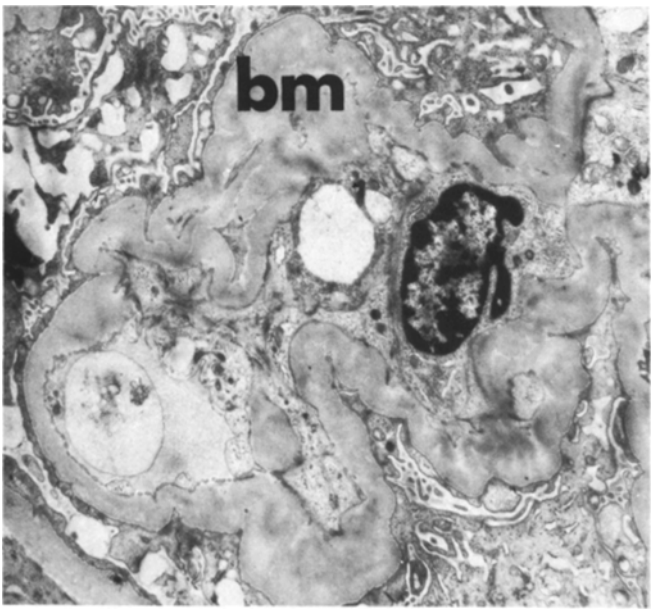

Fig. 1. Peripheral glomerular basement membrane (*bm*) distinctly thickened in a biopsy taken 13 days after the onset of fever. No deposits are seen. Magnification ×5000

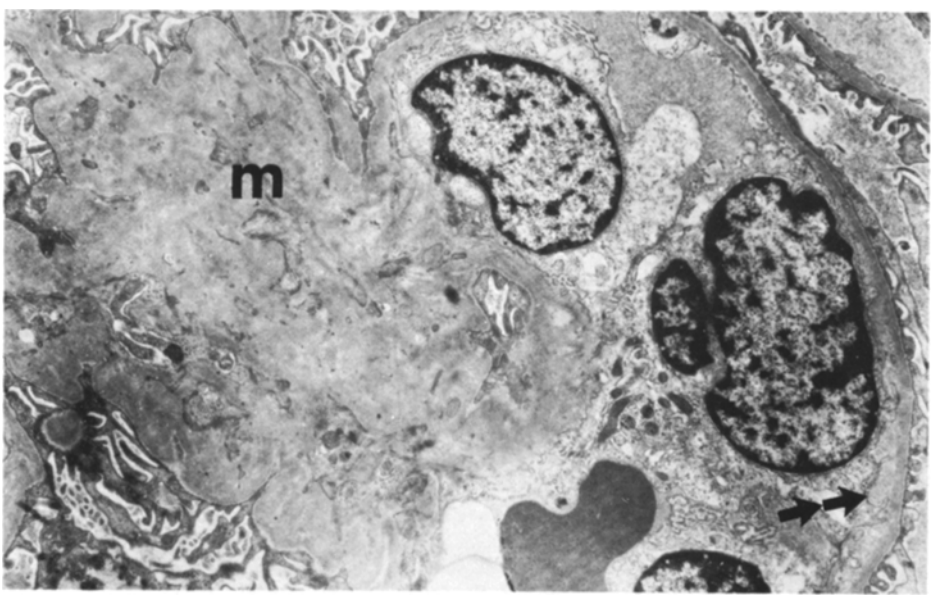

Fig. 2. From a glomerulus 19 days after the onset of fever. Mesangium (*m*) is more prominent than normal and shows folds at the periphery. Mesangial matrix is increased. Double arrow shows light flocculent material between the glomerular basement membrane and the endothelial cell. Magnification ×4800

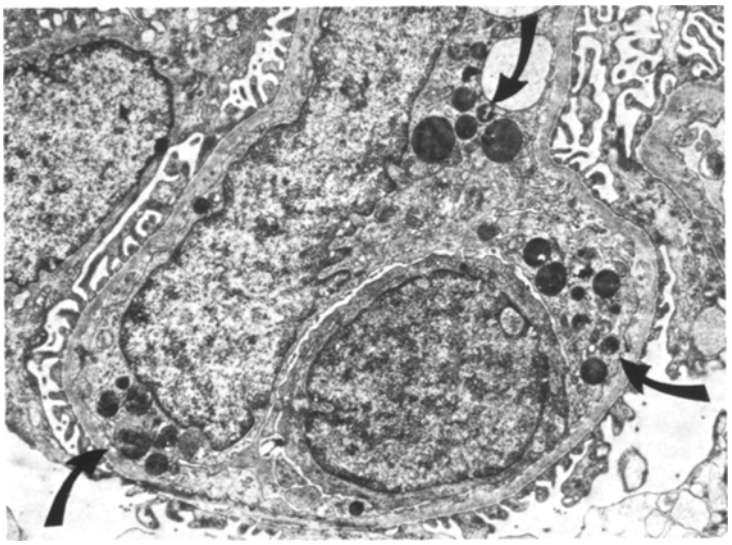

Fig. 3. From a glomerulus 14 days after the onset of fever. The glomerular basement membrane appears normal, but inside the capillary there are cells with large cytosomes (*arrows*) which suggest phagocytic activity. The cells are either monocytoid cells or phagocytic endothelial cells. Magnification $\times 5100$

All cases showed light flocculent subendothelial material on the luminal side of the glomerular basement membrane (Figs. 2, 5A). Dark deposits in the mesangium were seen on or later than the sixth day after the onset of fever in eight cases. Such deposits were not seen in the latest case of our material. The mesangial deposits usually were seen at the mesangial cell processes as dark granular material and only occasionally as large masses in the mesangium (Figs. 4–6). Most of our samples showed intramembranous granular deposits (Fig. 5C). Subepithelial deposits were seen in three cases and were most prominent in an biopsy taken 9 days after the onset of fever (Fig. 7). Deposits in the glomeruli were rare and thorough screening of numerous grids was generally necessary before they were found.

Various kinds of structures were found in association with the deposits. "Moon craters" were seen around intramembranous or subepithelial deposits (Figs. 7, 8B) in five of our cases (6–25 days after the onset of fever). These deposits also often contained membranous convoluted structures (Figs. 7, 8A, B), that could also be seen inside the thickened basement membrane without any deposits (Fig. 8F). Vesicular debris could be seen at the same areas (Fig. 8A).

Occasionally, dark masses were seen inside mesangial cells suggesting mesangial cell degeneration (Fig. 6C). Lighter areas in the abnormally prominent mesangium also demonstrated vesicular debris, possibly linked with a corresponding process (Fig. 6B).

Round extracellular particles in or on the epithelial side of the basement membrane were seen in nine cases and were not found in the two earliest

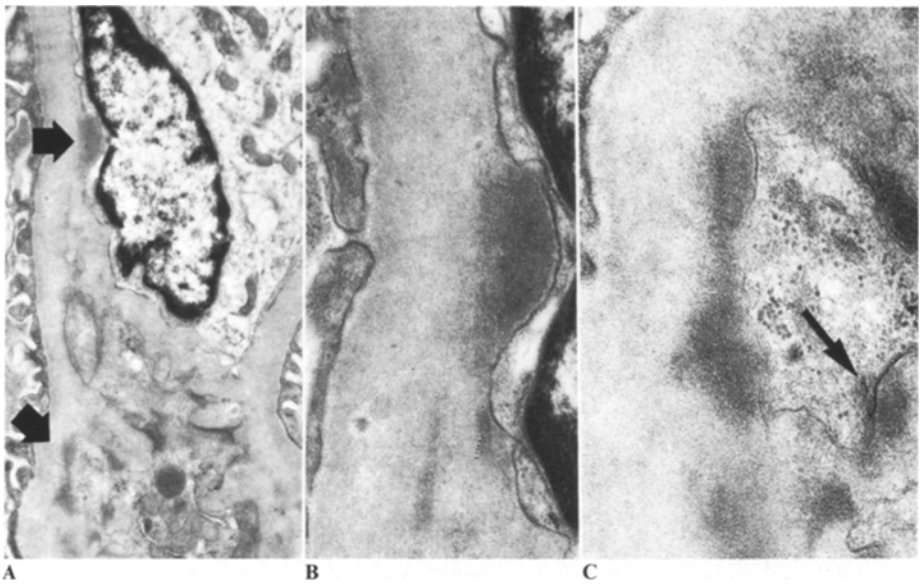

Fig. 4. **A** (left). Electron micrograph from a biopsy taken 6 days after the onset of fever. The arrows point at dark deposits at the neighbourhood of a mesangial cell and under an endothelial cell. Magnification ×7700. **B** (middle). The subendothelial deposit at higher magnification. The deposit is distinctly outside the cell between the cell membrane and the basement membrane. Magnification ×25,000. **C** (right). Deposits at the mesangial cell. Note the attachment body with distinct thickening of the plasma membrane and dark staining of the surrounding cytoplasm (*arrow*). There is a deposit outside the attachment body. Magnification ×31,000

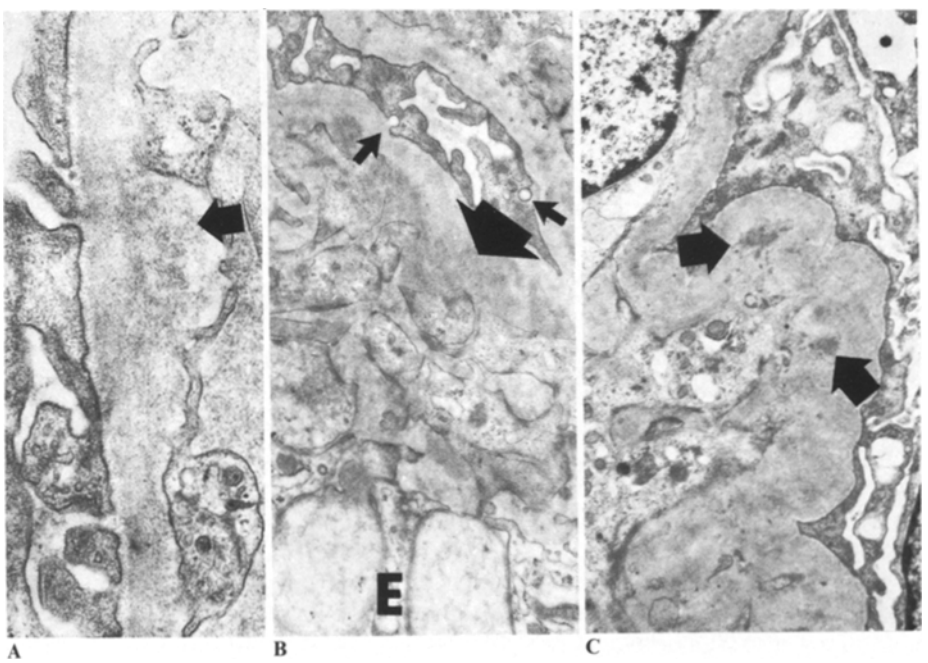

Fig. 5. **A** (left). Flocculent material (*arrow*) under the endothelium on the luminal side of the basement membrane 3 days after the onset of fever. Magnification ×23,000. **B** (middle). Mesangial deposit between mesangial cells and the mesangial basement membrane (*big arrow*) 6 days after the onset of fever. Smaller arrows show pinocytosis vacuoles under the epithelial cells. *E*=endothelial cell. Magnification ×10,500. **C** (right). Thickened mesangial basement membrane displaying dark deposits with irregular periphery (*arrows*) 6 days after the onset of fever. Magnification ×7700

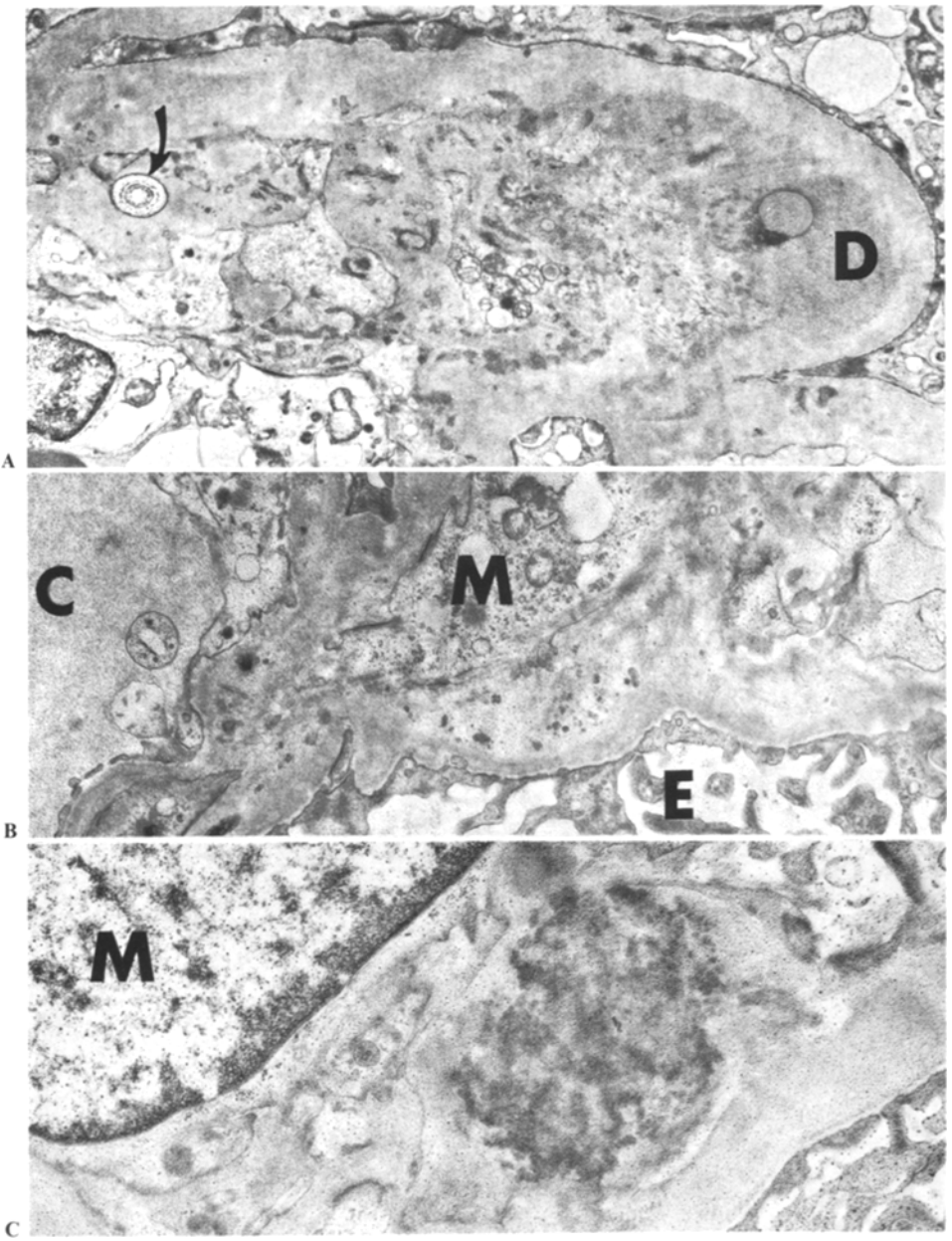

Fig. 6. A (above). Mesangial basement membrane near the hilus of a glomerulus 35 days after the onset of fever. There is a dark deposit (*D*) in the mesangium. At the arrow a laminated body in the mesangial matrix is seen. At the center there are cytoplasmic processes of mesangial cells and outside them in the matric dark granular material and membrane debris. Magnification ×6700. **B** (middle). Mesangial region in a glomerulus 11 days after the onset of fever. *C* capillary lumen, *E* epithelial side of the basement membrane, *M* a mesangial cell. Under the mesangial cell there is lighter-than-normal matrix with vesicular cell debris. Magnification ×9500. **C** (below). Mesangial region 14 days after the onset of fever. *M* mesangial cell. Note dark granular material in the matrix. The material probably originated from a mesangial cells as suggested by remnants of cell membrane seen around it. Magnification ×14,000

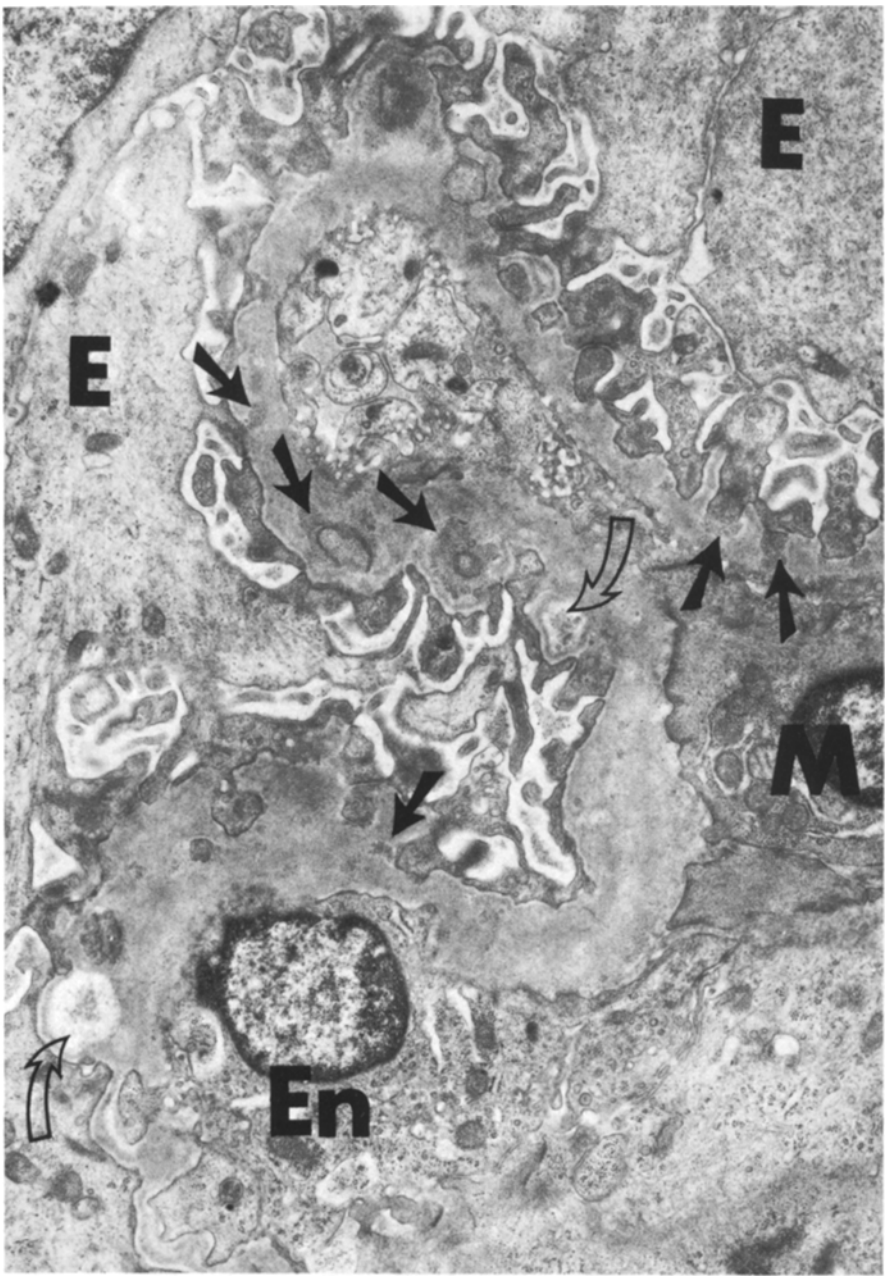

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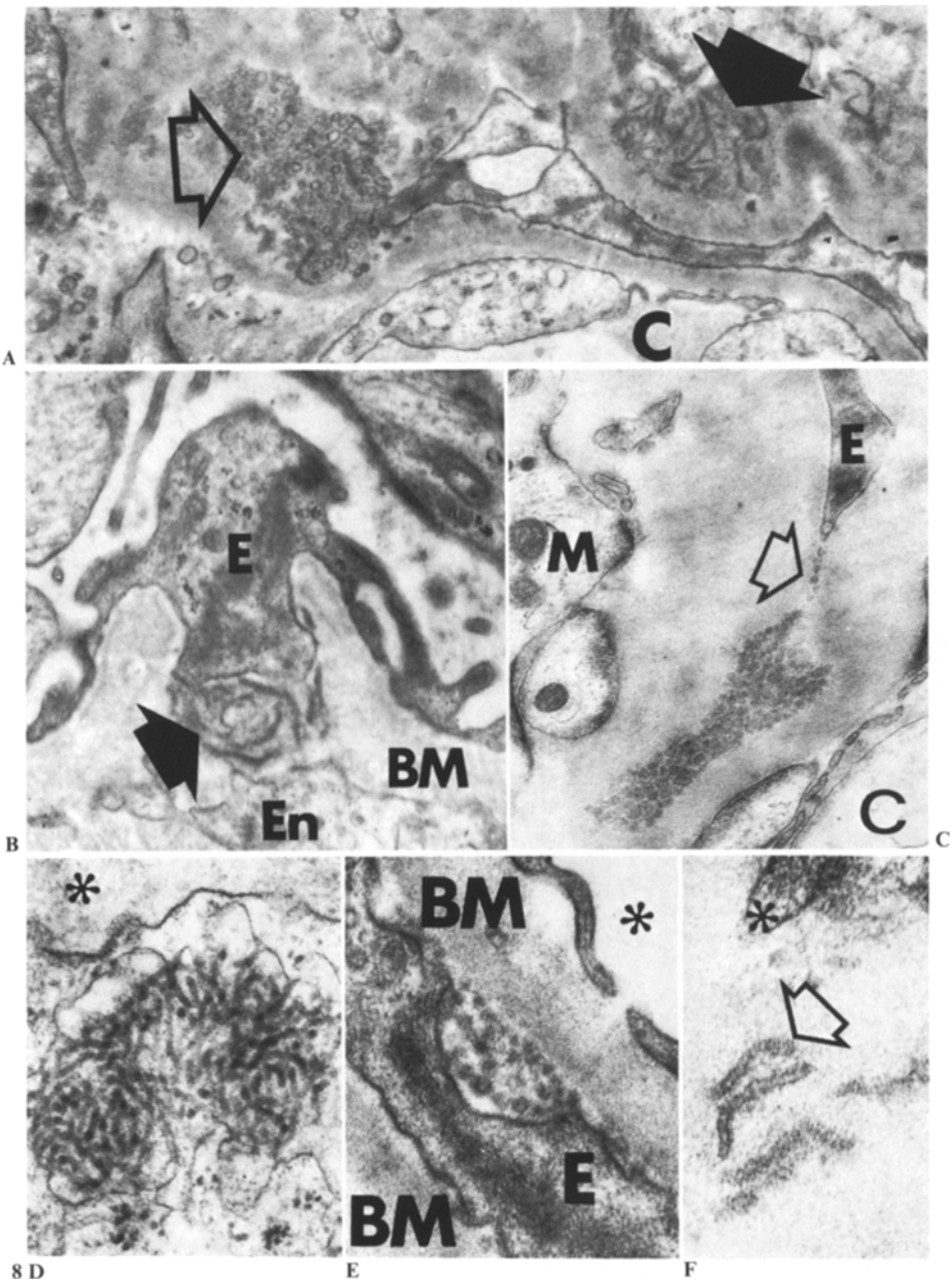
Fig. 7. Prominently altered basement membrane 9 days after the onset of fever. Part of the abnormal appearance is due to the level of sectioning, part due to the thickened basement membrane that shows irregular surface on the epithelial side of the membrane. Black arrows show subendothelial and intramembranous deposits (with occasional membranous convoluted structures). Open arrows point at light areas in the GBM that may show darker granular material at the center. *E* epithelial cell, *En* endothelial cell, *M* mesangial cell. Magnification $\times 12{,}500$

Fig. 8. A (above). Vesicular (*open arrow*) and tubulomembranous (*black arrow*) cell debris inside the thickened mesangial basement membrane 9 days after the onset of fever. Note the continuity of the vesicular debris with a process of an epithelial cell. *C* glomerular capillary. Magnification $\times 14{,}000$. **B** (middle, left). Nine days after the onset of fever. A typical "moon-crater" with the basement membrane (*BM*) around a foot process of an epithelial cell (*E*). There is membranous



debris (*dark arrow*) under the foot process. *En* endothelial cell. Magnification ×19,000. **C** (middle, right). Round extracellular particles in the mesangium 13 days after the onset of fever. At the top there is a process of an epithelial cell (*E*) that penetrates deep into the mesangial basement membrane. From its tip a line of particles can be followed to the larger group of particles. *M* mesangial cell, *C* capillary. Magnification ×19,000. **D** (bottom, left). Intraendothelial microtubular inclusions inside an endothelial cell in a glomerular capillary 13 days after the onset of fever. The asterisk in the capillary lumen. Magnification ×49,000. **E** (bottom, middle). Cytoplasm of the epithelial cell between two leaves of glomerular basement membrane (*BM*). Between the epithelial cell (*E*) and the basement membrane there are round extracellular particles. The asterisk is in the capillary lumen. From a sample taken 9 days after the onset of fever. Magnification ×41,000. **F** (bottom, right). Membranous convoluted structures in the mesangium (*open arrow*) 13 days after the onset of fever. Note the typical cross-striation. The asterisk shows a process of a mesangial cell. Magnification ×52,000

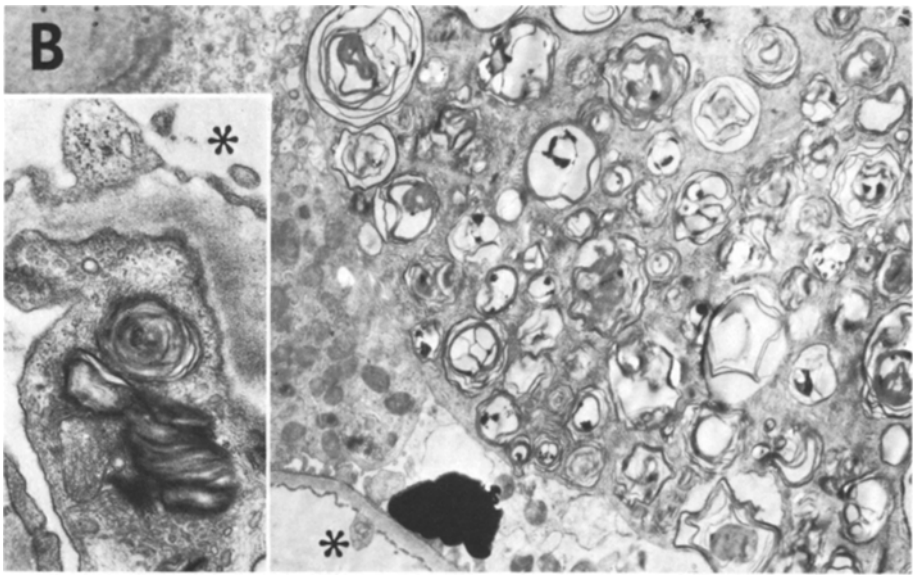
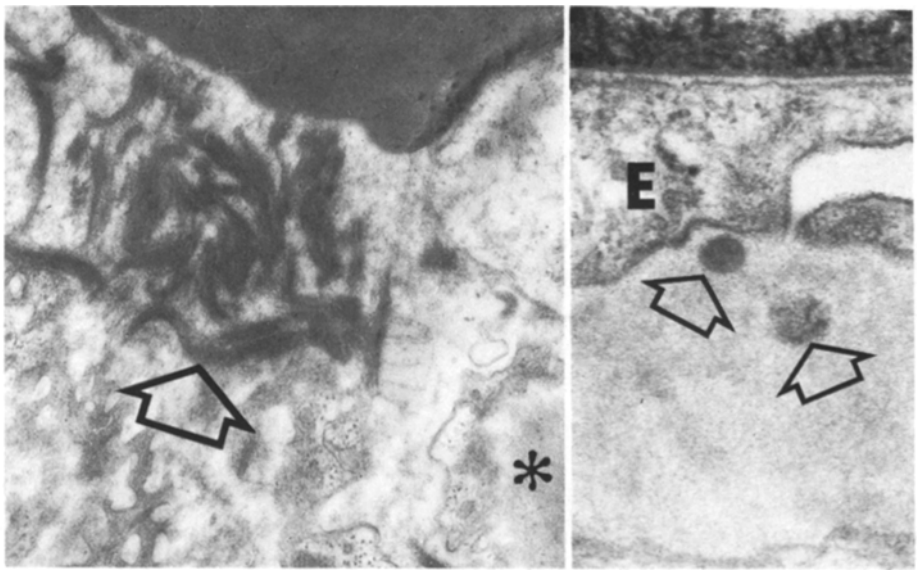


Fig. 9. Cytoplasm of a highly abnormal epithelial cell of the capsular epithelium in a biopsy taken 3 days after the onset of fever. The cytoplasm is filled with myelin bodies. *B* Capsular membrane. Asterisk in the lumen of the glomerular capillary. Magnification ×4300. The inset shows corresponding bodies in an epithelial cell of the glomerulus in the same patient. Magnification ×12,500



A B

Fig. 10. A (left). From a biopsy taken 9 days after the onset of fever. There are bundles of fibrin filaments in the capillary lumen (open arrow). Asterisk shows the site of the basement membrane. Magnification ×20,000. **B** (right). Dark intramembranous oval bodies (*open arrows*) on the epithelial (*E*) side of the basement membrane. Magnification ×80,000

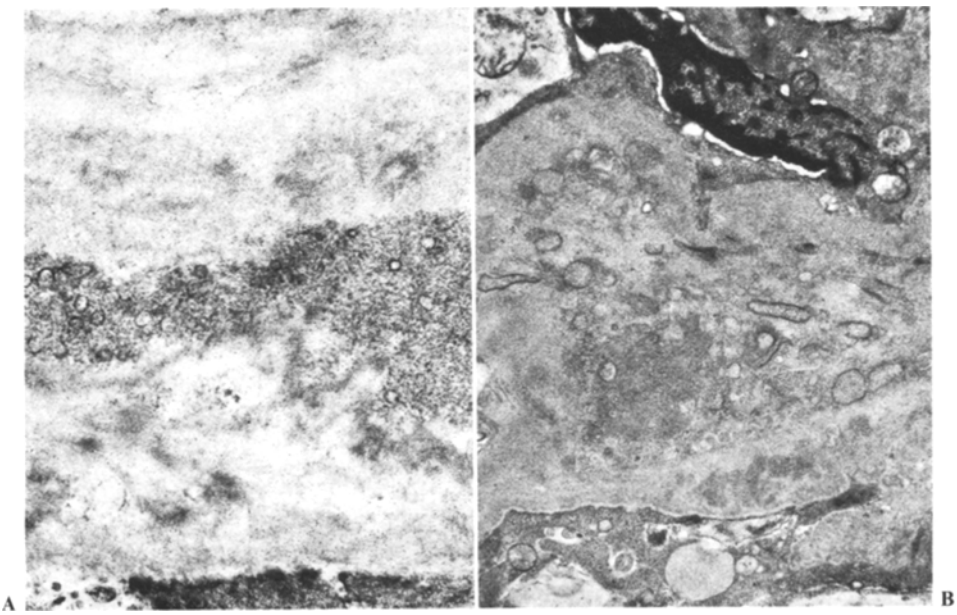


Fig. 11. A (left). Dark granular deposit with small membrane vesicles in the Bowman's membrane. Magnification ×22,000. **B** (right). Deposited material in the Bowman's membrane. Membrane debris is included in the deposit. Magnification ×9500

and latest samples of our study (Figs. 8C, E). Intraendothelial microtubular inclusions were seen in five of our cases (Fig. 8D).

Oval dark bodies, about 0.11 μm in the largest diameter (Fig. 10B) inside the GBM were seen in all of our cases as were pinocytosis vacuoles at the epithelial aspect of the basement membrane (Fig. 5B). Larger laminated bodies could occasionally be seen in Bowman's capsule or in the mesangium (Fig. 6A). One of our samples displayed dark fibrillar material (probably fibrin) inside glomerular capillaries (Fig. 10A) but aggregation of thrombocytes was not found in glomerular capillaries.

A peculiar type of change in a few cells of the capsular epithelium or the glomerular epithelium was seen in two patients. The cytoplasm of the cell contained numerous myelin bodies (Fig. 9). Dark granular deposits (Fig. 11A), often with membrane debris (Fig. 11B), were seen in the capsular basement membrane.

Discussion

Our immunohistochemical study (Jokinen et al., 1977) suggested that glomerular immune complexes are involved in Nephropathia epidemica. There are numerous findings in the electron microscopy of the condition which support this conclusion. Deposits are seen in the mesangium in immune complex diseases (Churg and Grishman, 1972), and increased amounts of material from the circulation enter

the mesangium in glomerular diseases (Stilmant et al., 1975; Hoyer et al., 1976). In Nephropathia epidemica small deposits were seen at the mesangial cell membrane outside the attachment bodies. The attachment bodies also appeared more prominent than usual; a change described by Gabbiani et al. (1975) fifteen days after injecting hyperimmunised rabbits with ferritin. Deposits of corresponding size were seen in the thickened basement membrane, often showing irregular outline, which suggested partial degradation – a process taking place in immune complex nephritis (Churg and Grishman, 1972).

The lumpy mesangial deposits are usually seen in chronic conditions, but in Nephropathia epidemica they seem to present heavy local deposition of material containing immunoglobulins in the acute phase of the disease.

Subepithelial deposits are found in various models and types of glomerular disease (Ehrenreich and Churg, 1968; Laguens and Segal, 1969; Kuriyama, 1973; Finlayson et al., 1975). Deposits with similar appearance may occur in patients suffering from acute viral hepatitis (Eknoyan et al., 1972). Subepithelial or intramembranous deposits were often associated with "moon craters" which occur also in diabetes (Østerby Hansen and Olsen, 1967; Østerby, 1972), and other diseases (Sakaguchi et al., 1965). Tallqvist et al. (1976) considered such indentations as remnants of former subepithelial deposits. These changes were not described by Jørgensen (1966), which suggests that they are not found in patients without clinical evidence of kidney disease. However, Tallqvist et al. (1976) found these changes in one of their 8 control subjects. The suggestion by Tallqvist et al. (1976) that indentations are remnants of former subepithelial deposits is in favour of the view that they are chronic in nature. In Nephropathia epidemica these changes can either develop in acute disease or do not appear to be linked with the pathogenesis of the condition.

The light flocculent deposits that we found in a subendothelial location in the peripheral capillaries (Fig. 5A) may contain immune complexes. Similar findings have been interpreted that way in studies on transplant kidneys (Porter et al., 1968; Andres et al., 1970; Hulme et al., 1972; Olsen et al., 1974) and in other studies (Sakaguchi et al., 1965; Zollinger and Gaboardi, 1971; Dillard et al., 1975).

Intravascular fibrin that was found in one of our patients suggests that intravascular coagulation takes place in Nephropathia epidemica. Decrease in blood platelets – a typical clinical feature – might be linked with this and be due to peripheral consumption of platelets. The bone marrow changes in Nephropathia epidemica support this view (Lähdevirta, 1971). Intravascular fibrin is found in serum nephritis, a feature linking NE with diseases caused by immunecomplexes (Chase et al., 1972).

Proliferation of cells in the glomeruli is not common but occurs in NE (Lähdevirta, 1971). This finding is in accordance with the immunohistochemical results which suggested scanty deposition of immunoglobulins in the glomeruli (Jokinen et al., 1977). We could not show prominent cell proliferation in electron microscopy, but found granulocytes and phagocytizing cells (possibly monocytes) in the capillaries. This finding supports the idea that immune phenomena are involved (Kondo and Shigematsu, 1972).

The thickening of the basement membrane and prominence of mesangial areas might be due to deposition of basement membrane-like material, such

as that seen under the endothelial cells along the peripheral capillaries (see above). Because the material often contains cell debris, degenerative processes are also taking place. The folds in the basement membrane at the mesangium might be due to contraction of the mesangial cells (Becker, 1972) but also suggest stickiness of the membrane that might result in fusion of membrane leaves under suitable conditions.

Cell debris composed of vesicles and membrane fragments in the mesangial areas, in the thickened parts of the membrane or in the lighter-than-normal areas of the thickened basement membrane is found e.g. in membranous glomerulonephritis (Ehrenreich and Churg, 1968), or transplant kidney (Hulme et al., 1972). Such debris is also seen in obsolescent human glomeruli (Nagle et al., 1969). This material probably originates from glomerular cells.

Many pathomorphological changes that we found need not necessarily be linked specifically with Nephropathia epidemica. Thus the deposits in the Bowman's membrane are of no diagnostic value even though probably more common in NE than in normal samples (Lähdevirta, 1971). We have seen similar deposits in a vast variety of conditions in clinical kidney biopsies, and in our understanding Jørgensen's study (1966) on the normal human glomerulus shows them, or similar deposits, in a few micrographs.

At the indentations of the basement membrane membranous convoluted structures could be seen (Fig. 8F). These are found in connection with many glomerular diseases (Bariéty et al., 1974). The mesangial material in Figure 6C is probably related to extracellular granular material of Bariéty et al. (1974), also of unspecific nature.

The round extracellular particles or intraendothelial microtubular inclusions cannot be given any specific diagnostic meaning either as these have been reported in almost any kind of glomerular disease (Bariéty et al., 1973; Bariéty et al., 1974). Our findings suggest that the round extracellular particles originate from epithelial cells through a degenerative process.

The dark oval bodies (Fig. 10B) in GBM need not be pathological. After studying the micrographs in Jørgensen's thesis on normal glomeruli we have come to the conclusion that they might occur under normal conditions. The laminated bodies in GBM and Bowman's membrane have been reported in hepatic glomerulosclerosis (Sakaguchi et al., 1965; Fisher and Perez-Stable, 1968) or diabetes (Østerby, 1972) but their origin or morphogenesis is obscure.

The myelin bodies found in the epithelial cells (Fig. 9) have been described in Fabry's disease (McNary and Lowenstein, 1965; Churg and Grishman, 1975). Their origin is totally obscure. In our samples they were less numerous than in Fabry's disease, and only a few epithelial cells contained them.

Olsen et al. (1974) in their excellent study on renal allografts, described 5 types of changes in the glomeruli. Flocculent material under the endothelium, granular electron-dense material in the mesangial areas, aggregates of vesicles or convoluted membranous structures, and round extracellular particles on the epithelial side of the glomerular basement membrane were found also in NE. These parallel findings might suggest that separate individual morphological changes in the glomeruli are non-specific from diagnostic point of view.

Our findings support the idea that immune complexes are deposited in the glomeruli in Nephropathia epidemica. The short period of immune complex

deposition, about 10 days (Jokinen et al., 1977), explains why the changes are less marked than in many other types of immune complex disease. The amount of antigen freed during the primary (viral?) infection is possibly also less than e.g. in post streptococcal glomerulonephritis in which the period of deposition may last longer. In chronic immune complex diseases such as LED deposition of immune complexes may last for years and this mechanism produces more prominent morphological changes. Changes other than the apparent immune complex deposits themselves are probably caused by reactive processes after deposition or by the direct action of the presumed virus or alternative pathogenetic mechanism of this disease.

The viral etiology of Nephropathia epidemica has not been proven, but steps towards solution have been taken (Oker-Blom et al., 1977). We did not find viral particles in the glomeruli but an immune complex etiology with viral antigens is a good explanation for our immunological (Jokinen et al., 1977) and morphological findings. Similar findings have been described in dengue, a hemorrhagic fever of Southeast Asia (Boonpucknavig et al., 1976), which is a viral disease.

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