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Hereditary Nephronophthisis with a Life Span of Three Decades

Light and Electron Microscopical, Immunohistochemical, Clinical and Family Studies

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Summary. Familial nephronophthisis was diagnosed in a son and two daughters of a mother who herself died in uraemia at the age of 29 years. The son died at 33 years, two daughters are alive at 30 and 33 years. Our cases suggest a dominant autosomal type of inheritance because the mother married twice; the affected son was from the first marriage and the affected daughters from the second marriage. There was no known consanguinity between the parents. The pathogenesis of the disease can be explained by a slowly progressive process that leads to complete or partial obstruction of the tubules in the corticomedullary area, and also, therefore, to cystic dilatations. Histological evidence for this is provided by the proliferation of fibroblasts around the collecting ducts and other tubules, prominent thickening of the tubular basement membrane, and fibroblasts and collagen fibrils in or inside the thickened basement membranes. An ultrastructural description of affected kidneys is given.

Key words: Familial nephronophthisis – Medullary cystic disease of the kidney.

Introduction

Fanconi and his coworkers (1951) described a familial kidney disease that affected children and was fatal at the age of 4–14 years. Their original report described 7 cases with hyposthenuria and uraemia. Autopsy demonstrated interstitial and tubular changes with far advanced fibrosis of the kidney. The authors called this disease "familial juvenile nephronophthisis". Smith and Graham (1945) described a girl of 9 years probably affected by a similar disease, but with no evidence of a familial nature. At autopsy they found cysts in the medulla and called these "congenital medullary cysts of the kidney". Clark (1951) described two families with patients resembling those described above. Since these reports several clinically and histologically similar cases have been described in the literature (Axelsson and Ödlund, 1968; Bolletti et al., 1959;

Broberger et al., 1960; Chipail et al., 1973; Christiaens et al., 1964; Faigel, 1964; Gekle and Brunnberg, 1972; Giselson et al., 1970; Goebel and Baethke, 1969; Goldman et al., 1966; Hackzell and Lundmark, 1958; Handa and Tennant, 1968; Herdman et al., 1967; Hogness and Burnell, 1954; Holmgren, 1964; Hooft et al., 1959; Ivemark et al., 1960; Kobayashi et al., 1967; Lappi and Rapola, 1973; Ljungqvist et al., 1967; Mangos et al, 1964; Mongeau and Worthen, 1967; Pascal, 1973; Pedreira et al., 1968; Roschlau and Justus, 1964; Royer et al., 1963; Seifert et al., 1960; Spicer et al., 1969; Strauss, 1962; Sworn and Eisinger, 1972; v. Sydow and Ranström, 1962; Victorin et al., 1970). Both recessive and dominant modes of inheritance have been suggested (Victorin et al., 1970; Seifert et al., 1960; Mongeau and Worthen, 1967; Goldman et al., 1966; Fanconi et al., 1951; Mangos et al., 1964; Broberger, 1960; Axelsson and Ödlund, 1968), and sporadic cases have also been reported with no evidence of a hereditary trait (Strauss, 1962; Spicer et al., 1969; Pascal, 1973; Hogness and Burnell, 1954; Mongeau and Worthen, 1967; Lappi and Rapola, 1973; Faigel, 1964; Holmgren, 1964). More recently many authors have considered the two diseases (familial juvenile nephronophthisis and medullary cystic disease) as examples of one and the same disease (Victorin et al., 1970; Strauss and Sommers, 1967; Sworn and Eisinger, 1972; Pedreira et al., 1968; Mongeau and Worthen, 1967; Herdman et al., 1967; Handa and Tennant, 1968; Goebel and Baethke, 1969; Giselson et al., 1970; Gekle and Brunnberg, 1972; Axelsson and Ödlund, 1968).

In this report we describe a *family* with progressive kidney disease histologically similar to familial juvenile nephronophthisis. The affected patients have lived for about thirty years without treatment and developed renal insufficiency about that age. To elucidate the pathogenesis we have done histological, electron microscopical, immunohistochemical and family studies.

Family History

The affected patients in this family are the *mother* (No. 1 in the pedigree) and her three children. She also had a fourth child, who died at the age of 1 year of unknown causes. The eldest child (son) and the other two children (daughters) have a different father. The mother died from chronic renal disease in 1946 at the age of 29, and no other details are known of her illness. At the time of death her children were 9, 5 and 2 years old. The eldest son was adopted by another family in northern Finland – 500 kilometres from where the others lived (in southern Finland). However, all the siblings, at about the same age showed signs of kidney disease with similar clinical and histological findings.

There was no anaemia, proteinuria, polydipsia, thirst or other evidence of kidney disease in the children of the affected three patients; their ages varied from 5 to 13 years at the time of the study.

The details of other siblings of the mother's generation (Fig. 1) were as follows: – Four were alive and are 61, 48, 50 and 54 years old, without evidence of kidney disease. One sister died at the age of 37 years from pulmonary embolus (no other details known), another sister died at the age of six of tuberculous meningitis, and another at the age of 1 month of pneumonia.

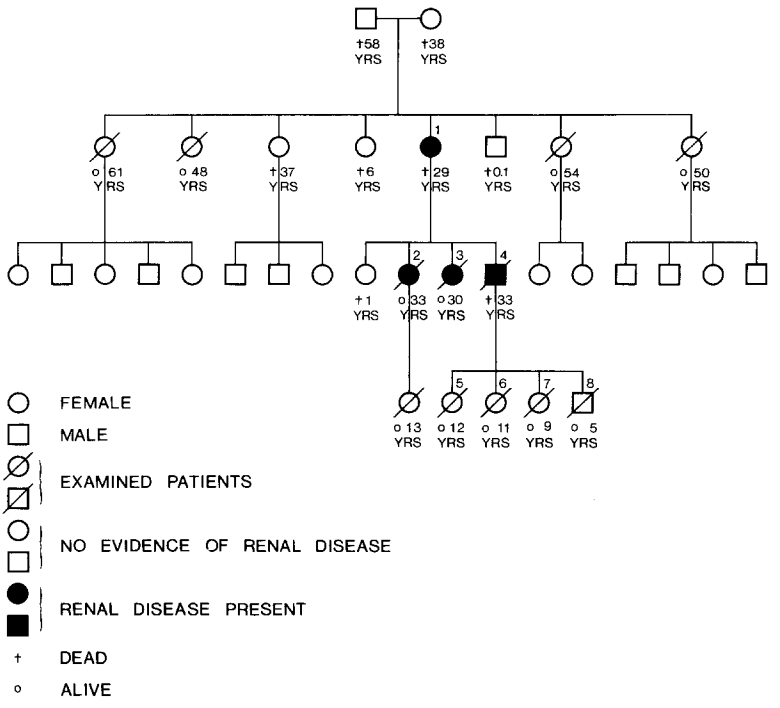

Fig. 1. Pedigree of the family under study

Case Histories

Patient 2. A male stoneborer, who had had intermittent proteinuria from the age of 17. At the age of 27, in 1966 he was admitted to the local Central Hospital in frank uraemia. After being treated six times with hemodialysis the creatinine clearance increased from 3.8 to 20 ml/min, serum creatinine dropped from 12.1 to 3.4 mg/dl and urea from 388 to 71 mg/dl. Urine volume increased from 1 to 5 l/24 h and he did rather well without further dialysis. He was continuously polyuric (up to 4–5 l/24 h) with good excretion of sodium (180 mEq/24 h), potassium (60 mEq/24 h) and chloride (150 mEq/24 h). The urine osmolality was 150 mosm/l. Retrograde pyelography was normal. His condition deteriorated during the summer and autumn of 1967, and he occasionally had episodes of unconsciousness. Serum creatinine increased to 8.9 mg/dl and creatinine clearance decreased to 9 ml/min. Urine volume was 2700 ml, with output of sodium 299, potassium 54 and chloride 225 mEq/24 h. From December 1967 he was on regular dialysis treatment until his death two years later. During that period his urine was analysed 48 times; proteinuria was found 9 times, an increased number of leucocytes 8 times and erythrocytes 3 times. Urine was cultured for bacteria 14 times and was always negative. With a planned renal transplantation in mind nephrectomy was done in March 1969 (left kidney) and in May 1969 (right kidney). The left kidney weighed 60 mg. The other kidney was roughly of the same size and weight. In both kidneys there were numerous scars on the surface and many cysts at the corticomedullary area (Fig. 2). Focally increased fibrous tissue could be seen on the cut surfaces. The cysts contained clear fluid. The capsule was thick and adherent to the surface of the kidney and to the perirenal fat. Blood pressure and the X-ray of the heart remained normal until July 69. Thereafter blood pressure increased to 140–190/100–120 mmHg, and left ventricular hypertrophy and congestive heart failure developed. He *died* in January 1970 at the age of 32. *Autopsy* showed pericarditis with adhesions and a 1 cm thick blood clot in the pericardial sack. The heart weighed 847 g and the wall of the left ventricle was hypertrophic (3 cm thick).

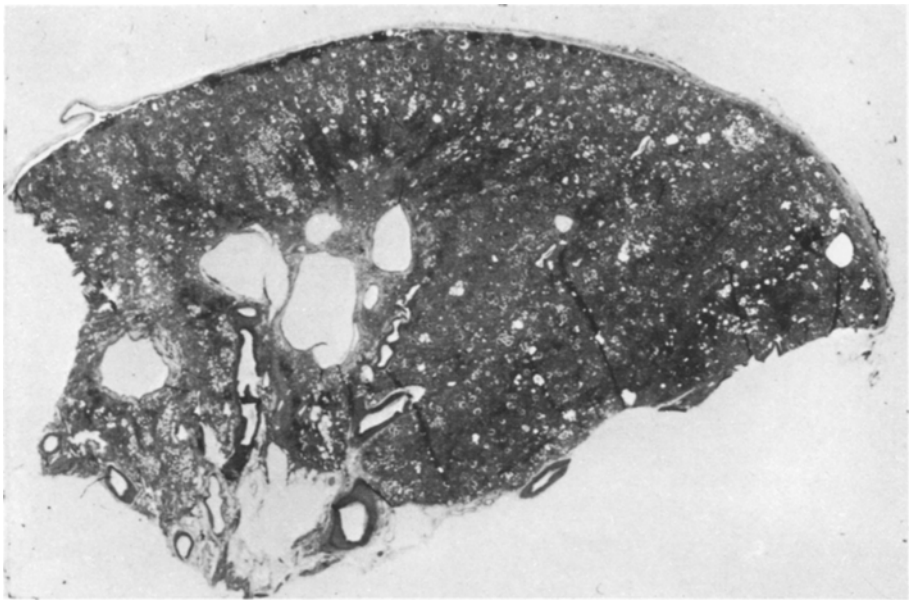

Fig. 2. Low power photograph of a section from an autopsy sample of the kidney showing large dilated cysts in the medulla or at the corticomedullary junction. There are also cysts in the cortex but these are much smaller. PAS-stain, magnification $\times 3.7$

There were no signs of infarction or coronary disease. The adrenals were larger than normal with a combined weight of 21 g. The spleen weighed 490 and was enlarged but the liver was of normal size. Other organs (brain, thyroid, hypophysis, lungs, large arteries, stomach and the intestines, gall bladder, pancreas, bone marrow) showed no abnormality.

Patient 3. A 33-year-old married female factory worker, sister to Patient 2, had occasional urinary infections and bouts of headache in her past history. Her serum creatinine was investigated in July 1972 and was found to be 3.3 mg/dl. The blood pressure had always been normal. In autumn 1972 the laboratory data were: Hb 12.1 – 9.6 g/dl, leucocytes 6400/mm^3, sodium 141 mEq/l, potassium 4.2 mEq/l, chloride 107 mEq/l, calcium 8.8 mg/dl, phosphate 3.7 mg/dl and alkaline phosphatase 43 U/l. Blood pH was 7.35, pCO_2/32 mmHg and base excess +3.0 mmol/l. White cell differential count showed an increased number of eosinophils (7%). Creatinine clearance was decreased: 47 ml/min. Midstream urine was investigated seven times. An increase in number of erythrocytes and leucocytes was found once and a significant number of bacteria twice. No proteinuria was present. On urography the kidneys were of normal size and shape but excretion appeared late. The calices were clumsy and clubbed, especially in right kidney. Radioisotope renography showed non-specific renal failure with slight impairment of urine flow on the left side. Bone X-ray was normal. Audiography revealed slight impairment in hearing of low sounds (up to 500 Hz). On ophthalmoscopy artery/vein ratio was 1:2. In January 1973 Hb was 10.1 g/dl and serum creatinine 4.6 mg/dl. Renography showed signs of progression of renal failure. Astrup examination showed metabolic acidosis: pH 7.28, pCO_2 41 mmHg and BE −6.8 mmol/l. She was put on a chronic hemodialysis program.

Patient 4. 30-year-old waitress, sister to Patients 2 and 3, had suffered from headache and backache since July 1972. Since August 1972 her blood pressure had been elevated (150 to 180/100–120 mm Hg). The laboratory data on the latter part of 1972 were: Hb 13.4, serum creatinine 2.6 – 2.1 mg/dl and creatinine clearance 31–34 ml/min. Serum sodium, potassium, chloride, calcium,

phosphate, alkaline phosphatase and electrophoresis were normal. Serum antinuclear IgM antibody titre was 1:20, but IgG titre was negative. Waaler-Rose and Latex tests were negative. Serum phosphate values were higher than normal (4.3 mg/dl). Protein and glucose were absent in repeated urine investigations, and there was no significant bacteriuria. Urine volume was about 2 l/24 h, and the specific gravity of urine 1.006–1.014. On angiography the renal parenchymal tissue was shown to be reduced and the course of the arteries was irregular, being bent around clear areas, which were apparently small cysts. Bone X-ray was normal. Renal failure progressed rapidly and cadaveric kidney transplantation was done in December 1974.

Results

Both kidneys of Patient 2 were available for histological studies. Patients 3 and 4 had a kidney biopsy. Two thirds of the biopsy was fixed in 4% formaldehyde, and embedded in paraffin. The rest was divided into two pieces for electron microscopy and immunohistochemical studies and handled as described

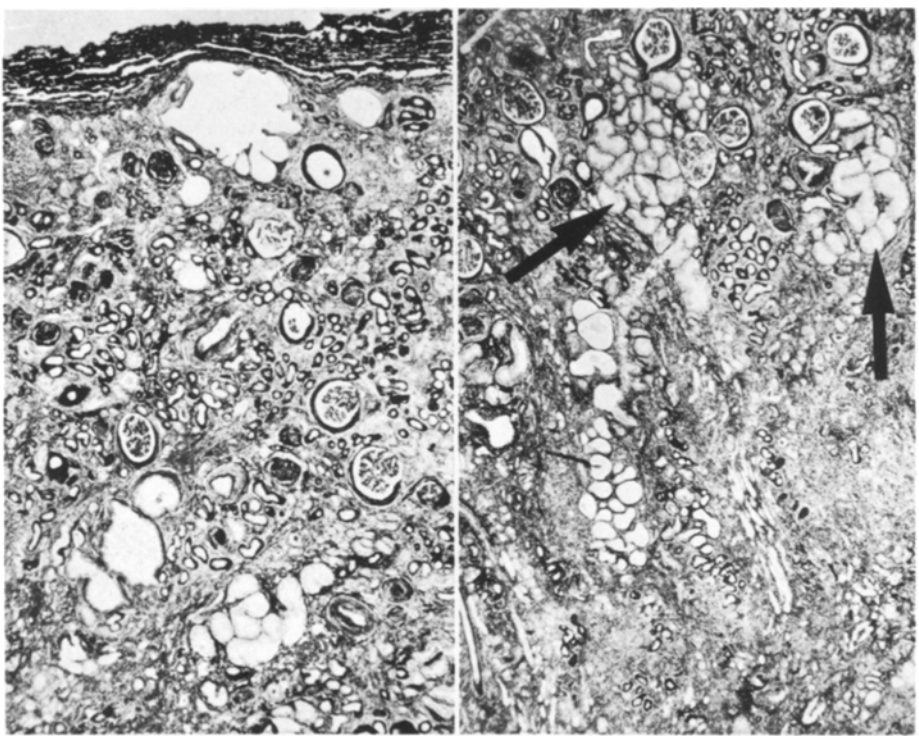

Fig. 3A and B. The microscopic appearance of the cortex and the corticomedullary area in patient 2. **A** Low power view of the upper cortex. Note the thickening of the basement membranes of the tubules and the Bowman's membrane. There is slight dilatation of the Bowman's space, destruction of numerous tubules and distinctly dilated groups of tubules. Magnification ×32 **B** Low power micrograph of the corticomedullary areas. Note the hyperplastic groups of tubules (arrows) and dilated tubules at the corticomedullary area. There is massive destruction of tubules at the lower parts of the figure with a lymphocytic infiltrate. Magnification ×31

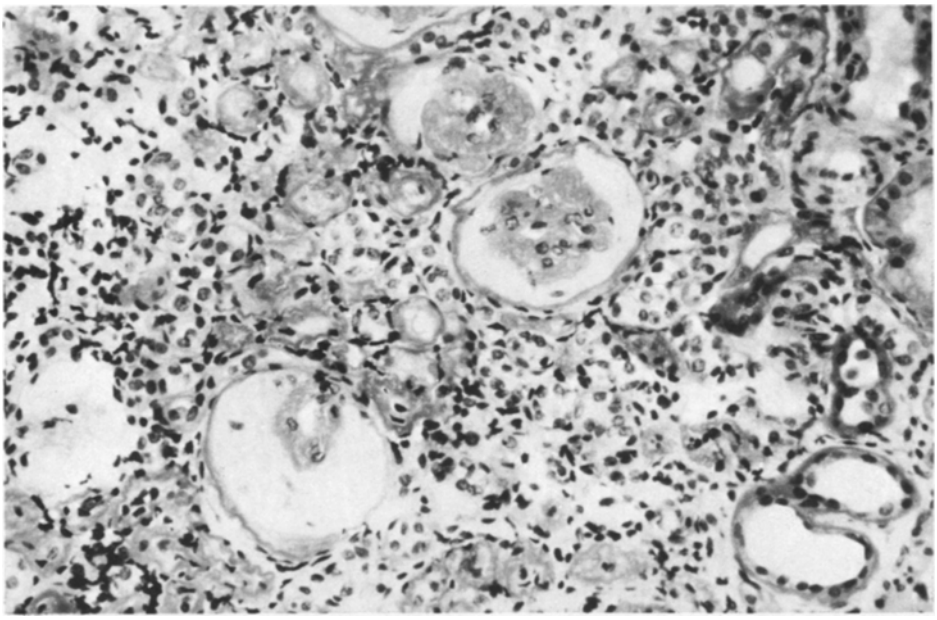

Fig. 4. High power micrograph of the cortex. Note the hyalinization of the glomeruli, widening of Bowman's space and aggregation of small atrophic tubules around the glomeruli with a slight inflammatory infiltrate. Many of the tubules show thickened basement membranes. PAS stain. Magnification ×220

earlier (Runeberg et al., 1971). The paraffin embedded material was sectioned at 3 μm, sections stained with H&E, van Gieson, PAS, PAS-Alcian Blue, silver methenamine and Gomori's trichrome stains. From samples embedded in Epon for electron microscopy 1 μm thick sections were cut and stained with 1% methylene blue for light microscopy.

Light Microscopy

About half of the glomeruli were hyalinized. Normal glomerular tufts were seen but there were usually mesangial sclerotic changes. Bowman's capsule was distinctly thickened in most glomeruli and parietal epithelial cells in occasional glomeruli were large and high. Amyloid was not found in any of the specimens.

Tubules around hyalinized glomeruli had disappeared, glomeruli were seen to be close to each other, usually separated by fibrotic interstitial tissue, atrophic convoluted tubules and interstitial lymphocytes. The atrophic tubules often had a thickened basement membrane. Around better preserved glomeruli there were highly convoluted hypertrophic tubules (Fig. 3). Dilatation of tubular structures was evident both in the cortex and in the medulla. There was slight dilatation of the Bowman's space around the better preserved glomeruli (Fig. 4). Both the hypertrophic tubules and occasionally the tubules with thickened basement

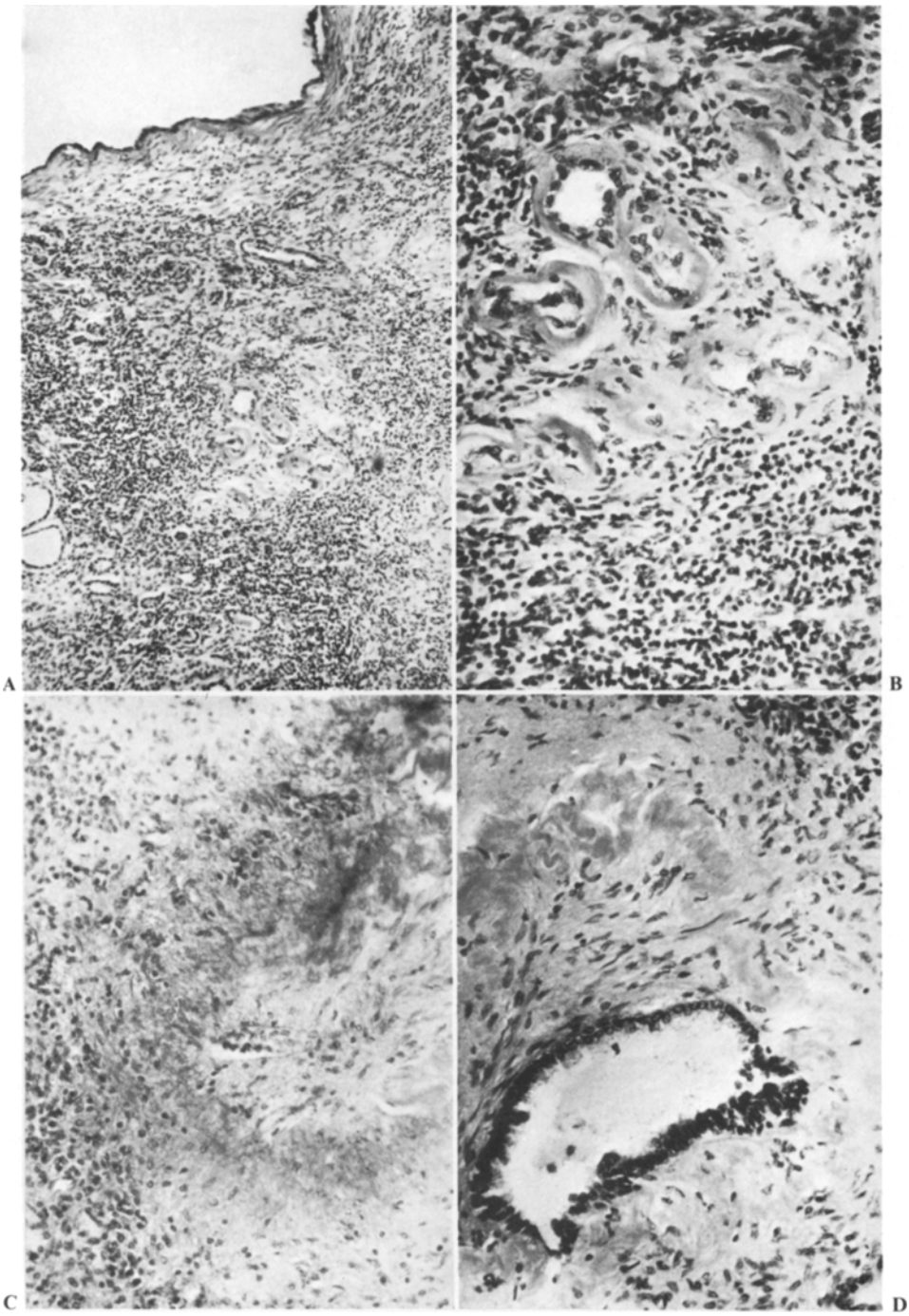

Fig. 5. A Low power micrograph of the renal medulla of patient 2. Dilated large cyst at the left. Note the increase in fibroblasts around the cyst and numerous fibroblasts between degenerating tubules with thickened basement membranes. There is a distinct lymphocytic infiltrate between the tubules. H&E stain. Magnification ×80. **B** Higher magnification from an area in Figure 5A. Degenerating convoluted tubules with an inflammatory infiltrate at the bottom and proliferation of fibroblasts at the top. HE stain. Magnification ×200. **C** Proliferating fibroblasts in the medulla. At the center there is a scarlike area with a collecting duct. Note the fibroblast surrounding the duct. PAS stain. Magnification ×140. **D** Collecting duct in the medulla. Note the proliferating fibroblasts inside and outside the degenerating basement membrane. The occurrence of fibroblasts between the epithelium and the basement membrane is common in this disease. H&E stain. Magnification ×200

membranes in the cortex were slightly dilated. There were small subcapsular cysts – often in groups of 2 to 4 – in the cortex, lined by flattened cuboidal epithelium. Many of these were multilocular, filled with PAS-positive granular or homogeneous material and situated in the immediate neighbourhood of tubules with thickened basement membranes. Similar multilocular cysts or groups of cysts were also seen deeper in the cortex. The cysts found at the corticomedullary area were different in appearance. These were large, not distinctly multilocular and contained clear fluid. They were surrounded by fibrous tissue that continued uninterruptedly as the interstitial tissue of the medulla and was composed mostly of fusiform fibroblasts with occasional scattered lymphocytes and granulocytes (Fig. 5). The epithelium in smaller cysts was distinctly cuboidal and very much like the epithelium in collecting ducts. In the largest cysts the epithelium was more flattened, however, probably due to the massive dilatation.

In the interstitium plasma cells were scarce and foam cells could not be seen. Arteries and arterioles showed slight intimal and medial hyperplasia. The juxtaglomerular apparatus was not prominent. There were homogeneous casts in occasional tubules in the lower cortex and corticomedullary area. A few tubules showed calcification.

Immunohistochemistry

There were no IgG, IgM, IgA, fibrin or complement deposits detected by immunofluorescent techniques in the glomeruli or elsewhere in the kidney tissue.

Electron Microscopy

The two biopsy pieces (Patients 3 and 4; Fig. 1) were from the kidney cortex. One biopsy contained 20 glomeruli, the other 7 glomeruli. There were no large cysts but dilatation of numerous tubules was seen. No dense deposits were seen in the glomeruli (Fig. 6). In many glomeruli the basement membrane was normal, in others there was thickening of the BM in the mesangial areas, increase in mesangial matrix material and widening of the mesangium or complete hyalinization of the glomerulus. No cell proliferation was seen and endothelial, mesangial and epithelial cells appeared normal. Small lipid vesicles of unspecific nature (Bariéty, 1974) were seen in and at the basement membrane. The thickened Bowman's membrane displayed granular deposits of non-specific type. Endothelial cells occasionally showed autophagic vacuoles with degenerated membrane material (myelin figures). Increased amounts of collagen were seen around the glomeruli and between the tubules. The interstitial reaction consisted of lymphocytes, fibroblasts, and macrophages. Plasma cells and granulocytes were rare. The basement membrane was thickened especially around small atrophic tubules with light staining cuboidal epithelial cells. The lumen was often not patent and the cytoplasm of the lining cells contained aggregates of lipofuscin-like material. In most of these cells there was a Golgi apparatus, bundles of cytoplasmic fibrils at the basal parts of the cell, small numbers

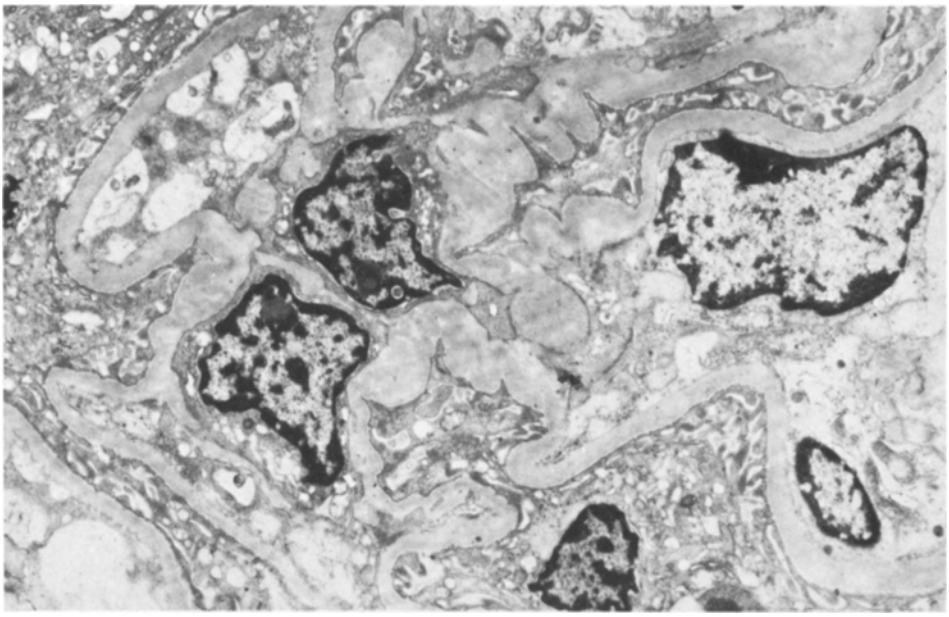

Fig. 6. Electron micrograph of a glomerulus in a kidney biopsy from a patient suffering from nephronophthisis. Note the thickening of the basement membrane at the mesangium and the absence of any deposited material at the basement membrane. Magnification $\times 6200$

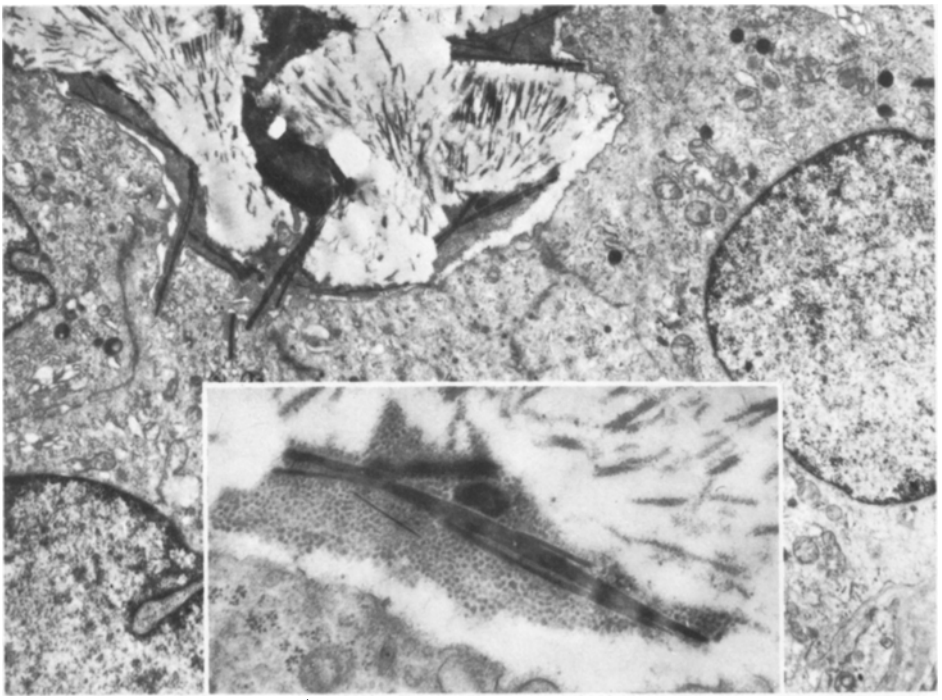

Fig. 7. A distal tubule with dark granular intraluminal material. There are numerous crystal-like structures in the lumen. Magnification $\times 65{,}000$. Inset: Higher magnification of the crystal-like structures embedded in the granular material. Magnification $\times 22{,}000$

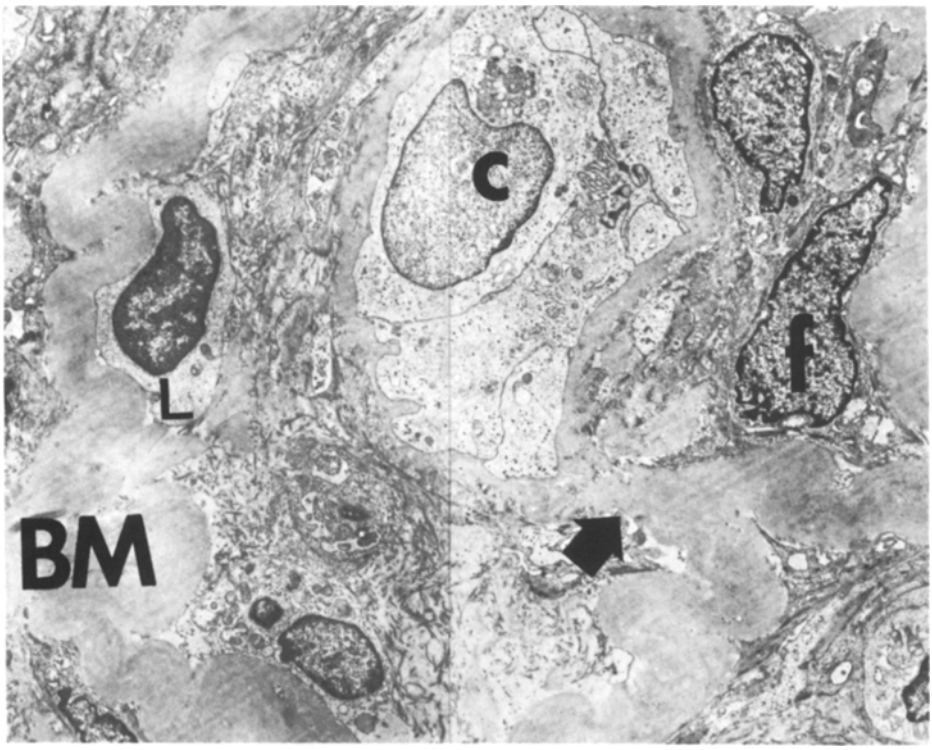

Fig. 8. An area of tubular destruction in the cortex. Note the thick basement membranes (*BM*), joined in places (arrow). Between the membranes there are collagen fibrils, fibroblasts (*f*) and lymphocytes (*L*). The appearance of the tubular cells (*C*) suggests that they are cells of the loop of Henle. The changes suggest that most tubular cells have died and disappeared and only a group of inactive cells (*C*) are left. Magnification $\times 4500$

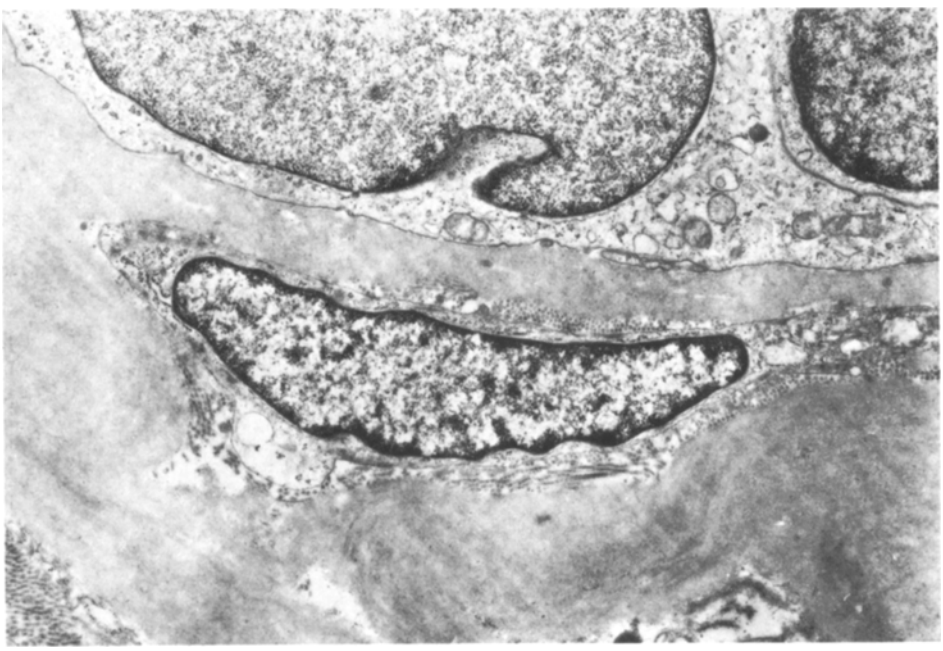

Fig. 9. A fibroblast inside the thickened basement membrane of a tubule probably from the distal parts of the nephron. Note the collagen fibrils around the cell body. Magnification $\times 11{,}000$

of polysomes, rough or smooth endoplasmic reticulum, and occasional cytosomes and apical light or dark vesicles. The lateral borders of the cells usually showed an abscence of membrane infoldings.

The epithelial cells of dilated tubules were high, the cytoplasm was rich in polysomes and mitochondria and the luminal surface showed occasional cytoplasmic projections. Even greatly dilated tubules showed signs of differentiation of the luminal membrane such as occasional cilia. In less dilated tubules basal infoldings were seen, and occasional necrotic nuclei were observed among epithelial cells. A few tubules contained apparently coagulated material, occasionally with slender crystals in close proximity to the epithelial cells (Fig. 7).

In greatly thickened basement membranes fibroblasts, lymphocytes and even plasma cells could be seen. There were also collagen fibre bundles in and around these membranes. This suggested a constricting process around the tubules. It appeared as if the changes were produced by destruction of the tubules with only a few tubules or groups of tubular cells having been left alive in the corticomedullary area (Figs. 8 and9). Occasionally the thickened basement membranes contained grey granular deposits.

The cells of the slightly dilated proximal tubules displayed a brush border, a large number of apical vesicles and numerous cytosomes. The cells, however, were thinner and contained less mitochondria than normal proximal tubule cells. In more dilated tubules the cells appeared to have lost most of their brush border and cytosomes, appearing more like distal tubule cells. Occasional tubules were filled with cell debris.

Discussion

A review of the literature favours the idea that familial nephronophthisis and medullary cystic disease are one and the same disease. In our discussion we will call this disease nephronophthisis. In Table 1 we have grouped the available data which should give an idea of the mode of inheritance providing that all the cases are examples of the same genetic disease. With autosomal recessive type of inheritance about $^1/_4$ of the patients should be affected. However, in the above groups the ratio affected children/all children is about $^1/_2$. This is what would be expected in case of autosomal dominant mode of inheritance. Our family further suggests an autosomal dominant type of inheritance because the affected mother was married twice and transferred the disease to her children in both marriages. That the ratios in Table 2 are above 0.5 is due to the exclusion of reports on sporadic cases, which generally did not give enough data for calculations. A dominant X-linked mode of inheritance is not possible, because there are three families with an affected father who has transferred the disease to his sons (Mongeau and Worthen, 1967; Pedreira et al., 1968; Victorin et al., 1970). There is a certain sex-linked pattern, however. In the affected families the sick parent is usually the mother (11 out of 15 families). There is also a distinct female predominance in the number of affected children, suggesting that the female sex is more susceptible to the disease. This is most clear in families where one of the parents is affected. A polygenic type of inheritance

Table 1. Nephronophthisis families presented in the literature with healthy consanguineous parents, healthy non-consanguineous (or not-known-to-be consanguineous) parents, and families with one of the parents suffering from nephronophthisis. The table shows the number of families, number of children in the families, number of affected children and the proportion of those affected among female or male children. The numbers of the two last columns do not necessarily agree with those of the two former columns because many studies do not mention the sex of the children

Families	No. of families	No. of children	No. of affected	affected males/ all males	affected females/ all females
Healthy, consanguineous parents[a]	3	20	12	7/11	5/9
Healthy, nonrelated parents[b]	33	129	66	27/58	35/61
One of the parents has nephronophthisis[c]	15	57	31	12/26	19/31

[a] Fanconi et al., 1951; Hooft et al., 1959; v. Sydow and Ranström, 1962

[b] Bolletti et al., 1959; Chipail et al., 1973; Christiaens et al., 1964; Fanconi et al., 1951; Gekle and Brunnberg, 1972; Giselson et al., 1970; Goebel and Baethke, 1969; Goldman et al., 1966; Hackzell and Lundmark, 1958; Handa and Tennant, 1968; Herdman et al., 1967; Kobayashi et al., 1967; Lappi and Rapola, 1973; Mangos et al., 1964; Mongeau and Worthen, 1967; Smith and Graham, 1945; Sworn and Eisinger, 1972; Victorin et al., 1970

[c] Axelsson and Ödlund, 1968; Goldman et al., 1966; Mongeau and Worthen, 1967; Pedreira et al., 1968; Victorin et al., 1970; our cases

Table 2. Ratios for affected children/all children, affected males/all males, affected females/all females in the nephronophthisis families published in the literature (see Table 1). The table also shows the ratio of affected fathers and affected mothers in families with one of the parents suffering from the disease

	Affected/ all children	Affected/ all males	Affected/ all females	Affected fathers/ affected mothers
Healthy, consanguineous parents	0.600	0.636	0.556	
Healthy, nonrelated parents	0.512	0.466	0.574	
One of the parents has nephronophthisis	0.544	0.462	0.613	4/11

is also possible. This is suggested by apparently sporadic cases of this disease (Strauss, 1962; Spicer et al., 1969; Pascal, 1973; Hogness and Burnell, 1954; Mongeau and Worthen, 1967; Lappi and Rapola, 1973; Faigel, 1964; Holmgren, 1964), families with healthy children, children with various ocular defects (e.g. retinal disease), children with nephronophthisis and children with both ocular disease and nephronophthisis (Meier and Hess, 1965; Senior et al., 1961). Most of the patients suffering from nephronophthisis are light or red haired (Rayfield and McDonald, 1972) and hair color exhibits a polygenic type of heredity pattern. The familical cases of nephronophthisis might show Mendelian patterns because of concentration of genes in these families.

Our findings give some clues to the pathogenesis of this disease. Immune complexes are not involved. We suggest that there is obstruction of urine flow

by a process acting in the medulla and at the corticomedullary area. Obstruction of urine flow is known to decrease the tonicity of the urine and decrease reabsorption of sodium (Berlyne and Macken, 1962). This is what is found in nephronophthisis before signs of uraemia develop. Thereafter this change is of non-specific nature (Kahn et al., 1972; Schultze et al., 1972).

Fibrosis and proliferation of fibroblasts at the corticomedullary area is one reason for obstruction. The same process could cause changes in blood flow and so result in further damage. In our cases, proliferation of fibroblasts was most prominent around the medullary collecting ducts and often inside the basement membrane. Similar findings were seen around other tubules with the thickened basement membranes containing fibroblasts and collagen fibres. The obstructive process will lead to dilatation or necrosis of the tubules and to hyalinization of the glomeruli. The proximal tubules will be affected first. Damage to the proximal tubules is prominent in this disease, and they are in fact spared in only a few nephrons.

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