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The Nephronophthisis Complex

A Clinicopathologic Study in Children

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Summary. The clinical and morphological findings are described in 27 children with nephronophthisis. Seventeen children were considered as sporadic cases. In 10 familial cases the presumed mode of inheritance was autosomal recessive. The clinical picture was rather uniform: polyuria-polydipsia, hyposthenuria, anemia, growth retardation, and azotemia with progressive renal failure. Six patients presented with tapeto-retinal degeneration. In a further seven children other ocular changes were detected. Two female siblings showed additional non-renal manifestations: mental retardation, pulmonary emphysema, skeletal anomalies, and congenital hepatic fibrosis.

Renal histology displayed a chronic sclerosing tubulo-interstitial nephropathy with extensive tubular atrophy and dedifferentiation. Medullary cysts were frequently found in end-stage kidneys. Immunofluorescence was either non-specific or completely negative. On electron microscopy, the tubular basement membrane changes predominated: thickening, lamellation, splitting, and deposition of microfibrils within the increased basement membrane substance. Detailed light- and electron microscopic findings were non-specific but the overall morphologic picture was characteristic and even diagnostic in conjunction with the clinical presentation.

A recurrence of nephronophthisis in transplanted kidneys has not been observed.

The pathogenesis of nephronophthisis is obscure but with respect to the morphologic findings a primary or secondary tubular basement membrane defect seems very likely.

Our experience suggests that nephronophthisis is a frequent cause of chronic renal failure in children and commonly associated with non-renal abnormalities. To avoid the separation of different syndromes presenting with a uniform renal disease but various non-renal manifestations, we suggest that the term "nephronopthisis complex" be used.

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Introduction

Juvenile nephronophthisis is a chronic tubulo-interstitial renal disease characterized by an early onset of polyuria and polydipsia, decreased concentration ability, anemia, growth retardation and progressive renal failure. It was first described by Fanconi et al. (1951) in seven children from two families. A clinically and morphologically very similar sporadic case had been reported previously by Smith and Graham in 1945. The authors found at autopsy numerous cysts in the renal medulla which they designated as "congenital medullary cysts of the kidneys".

Up to now, more than 300 patients have been reported, with what is generally described in the European literature as "juvenile nephronophthisis," or in the American Literature as "medullary cystic disease". Autosomal recessive and autosomal dominant modes of inheritance have been proposed in familial cases of both disorders. The two conditions cannot be distinguished on morphological grounds and also have many clinical features in common (Strauss and Sommers 1967; Mongeau and Worthen 1967; Pedreira et al. 1968; Alexander and Campbell 1970; Sworn and Eisinger 1972; Brouhard et al. 1977), suggesting that juvenile nephronophthisis and medullary cystic disease represent manifestations of the same nosological entity.

We report our experience in 27 children and adolescents with nephronophthisis followed from 1968 to 1980. The kidney pathology is analysed at different stages of the disease and diagnostic criteria are discussed. Our series demonstrates that juvenile nephronophthisis is a disorder which is not restricted to the kidney but is frequently associated with a variety of non-renal disorders, especially ocular changes.

Materials and Methods

For morphologic examination, kidney tissue was available from 8 percutaneous biopsies, 17 surgical biopsies, one nephrectomy specimen and 5 autopsies performed in 27 patients.

Renal tissue submitted for *light microscopy* was fixed for 6 h in Dubosq-Brazil fluid and subsequently for 24 h in 12% buffered formalin. Paraffin sections were stained routinely with hematoxylin and eosin, trichrome light green, periodic acid-Schiff with hematoxylin and chromotrope 2R silver methenamine. Congo red staining was performed in some cases.

For *immunohistologic examination,* the renal biopsy specimens from 9 patients were snap-frozen in isopentane chilled in liquid nitrogen. 3–5 μm cryostat sections were incubated with fluorescein isothiocyanate (FITC)-conjugated antisera to human IgA, IgG, IgM, Clq, C4, C3 and C9 (Behring-Werke, Marburg, FRG; Dakopatts, Denmark). Anti-properdin was kindly provided by Dr. Jungfer, Heidelberg (FRG).

Eight biopsies were examined by *electron microscopy*. The tissue was fixed in phosphate-buffered 2.5% glutaraldehyde, postfixed in OsO_4, dehydrated and embedded in Araldite. Semithin sections were stained with toluidine blue and paraphenylendiamine, ultrathin sections with uranylacetate and lead citrate as well as with silver methenamine.

Results

Clinical Presentation

The diagnosis of juvenile nephronophthisis was made on the basis of clinical and morphologic investigations in 20 (10%) out of 200 patients with chronic renal insufficiency observed from 1969 to 1980 at the University Children's Hospital in Heidelberg. Six additional cases were followed at the University Children's Hospital in Bonn and one patient at the University Children's Hospital in Erlangen.

Fourteen patients were male and 13 female. Their age at the time of the first clinical evaluation varied between 3 and 17 years (mean age 8 9/12 years). Seventeen patients (8 male, 9 female) had to be considered as sporadic cases, because no evidence of renal disease was found up to now in any of their relatives. In 10 children (6 male, 4 female) one or more siblings had signs of juvenile nephronophthisis (proven histologically in 8 cases) suggesting an autosomal recessive type of inheritance. Consanguinity between parents was never noted.

The *first symptoms* could be traced back to early childhood in most cases. They consisted of polyuria and/or polydipsia and were frequently associated with enuresis. The main features present at the time of first *clinical* evaluation are shown in Table 1. A failure to concentrate the urine above 800 mosm/l after 12 h water deprivation was found in all cases tested. Further manifestations included growth retardation, renal osteodystrophy, anemia with pallor and weakness, acidosis, and renal sodium wasting. Urine analysis revealed no, or only mild, proteinuria without hematuria or bacteriuria. In no case was there any anamnestic or clinical evidence of urinary tract infection, vesico-ureteral reflux, malformation of the lower urinary tract, or of tubulo-interstitial nephritis of toxic origin. Chromosomal studies were consistently normal. Signs of chronic renal insufficiency were observed almost constantly at the first clinical presenta-

Table 1. Initial *clinical* manifestations in 27 children with nephronophthisis

Symptoms	No of patients ($N=27$)
Polyuria and/or polydipsia	20
Hyposthenuria (maximal urinary osmolality <800 mosm/l after 12–14 h thirst)	14
Enuresis	7
Renal sodium wasting	3
Growth retardation (body height <3rd percentile for chronological age)	12
Anemia (hemoglobin <10 g/dl)	14
Chronic renal insufficiency (serum creatinine >1.5 mg/dl)	24

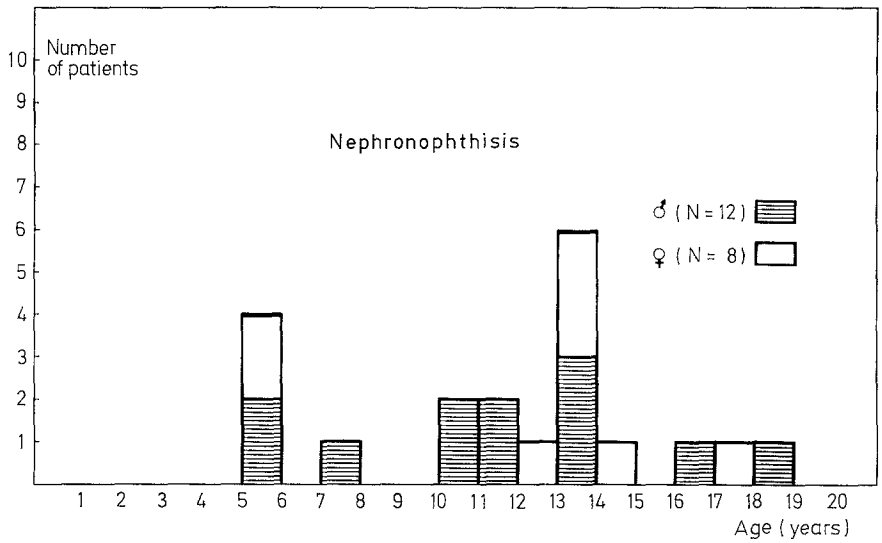

Fig. 1. Age at time of "renal death" (terminal renal failure) in 20 patients

Table 2. Course of chronic renal failure in 27 patients with nephronophthisis

Mode of treatment	Survivors	Deaths	Total
Conservative treatment	7	2	9
Hemodialysis	7	3	10
Transplantation	6	2	8
	20	7	27

tion when serum creatinine levels were above 1.5 mg/dl in 20 out of 27 patients. All children were normotensive except those in the terminal stage of renal failure.

The *clinical course* was progressive in all cases. Twenty patients have reached terminal renal failure within a period ranging between one year and 10 years after first clinical presentation. The average age at first dialysis or at death in non-dialysed patients was 11 6/12 years (range 5 to 18 years; Fig. 1). The modes of treatment at the last follow-up (April 1981) are summarized in Table 2. Six children have been transplanted successfully. No evidence of recurrence of the underlying disease was observed in these cases. Seven out of 27 children have died.

Non-renal Abnormalities

Thirteen children (8 male, 5 female) presented with non-renal abnormalities. A variety of *ocular* changes were noted in these patients (6 familial, 7 sporadic cases) including six children with various degrees of tapeto-retinal degeneration (Table 3).

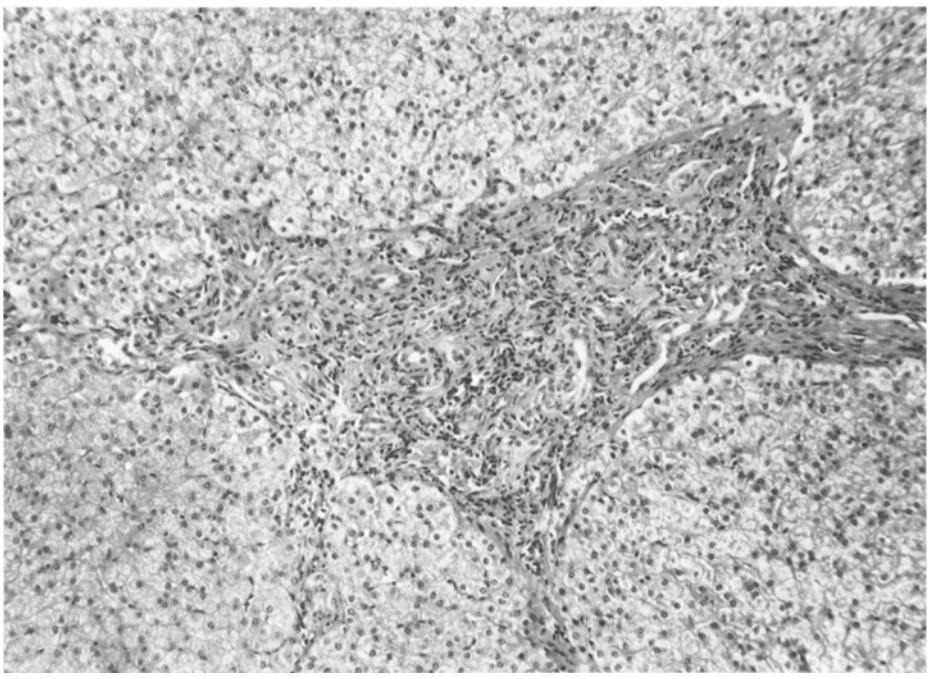

Fig. 2. Liver biopsy. Congenital hepatic fibrosis: enlarged portal tracts with fibrosis and slight bile duct proliferation. Trichrome stain, ×90

Table 3. Ocular changes associated with nephronophthisis in 13 out of 27 children (hypertensive retinopathy excluded)

Ocular change	No. of patients ($N=13$)
Tapeto-retinal degeneration	6
Nystagmus	6
Myopia	3
Coloboma	2
Strabismus	2
Hyperopia	2
Atrophy of the optic nerve	1
Amblyopia	1

Two female siblings who have been described elsewhere (Weber et al. 1979) showed a combination of retinitis pigmentosa, coloboma, liver fibrosis (Fig. 2), skeletal anomalies (kyphoscoliosis, short metatarsale IV), cerebellar ataxia, mental retardation and pulmonary emphysema (Table 4). In another sporadic case, liver fibrosis was present.

Light Microscopy

The kidney histology displayed, in the early stages, a focally accentuated, and in the advanced stage a diffuse sclerosing tubulo-interstitial process (Fig. 3).

Numerous tubules were atrophic and tortuous, predominantly those at the cortico-medullary junction. Atrophic tubules frequently showed diverticulum-like protrusions. The tubular basement membranes were extremely thickened and strongly PAS-positive (Fig. 4a). The thickening of the basement membranes was either segmental or circumferential, occasionally with nodular accentuation. In advanced stages the tubules were surrounded by two or even more layers of broadened and wrinkled basement membranes. Fibroblasts were noted between the membrane layers within intermembranous lacunae. Silver impregnation (Fig. 4b) showed various zones of argyrophilia within the basement membrane substance. Thickening of the basement membranes and diverticulum formation were most prominent in the distal tubules, particularly in the ascending limbs of Henle. In the advanced stages, tubular epithelial cells were dedifferentiated. Satisfactory anatomical identification of individual tubular segments was impossible in most instances. Tubular lumina were markedly dilated or completely collapsed, and only occasionally filled with homogenous proteinaceous casts. Thyroid-like pseudofollicular areas, considered by some to be characteristic of chronic pyelonephritis, were lacking.

Atrophic tubules were surrounded by collars of a dense fibrotic interstitial tissue accompanied by a sparse inflammatory infiltrate consisting of lymphocytes and histiocytes. Mononuclear cell infiltration was pronounced in areas of extensive tubular dissolution. Pseudolymphfollicular structures were extremely rare, and interstitial foam cells were never encountered. Lymph vessel casts were frequently noted, particularly in advanced stages of the disease.

Glomeruli were involved to a variable degree in the sclerosing process. They appeared either normal with thin basement membranes and delicate intercapillary axes, or showed circumferential periglomerular fibrosis with splitting and thickening of the Bowman's capsule. Thickening of the Bowman's capsular membrane was accentuated at the urinary pole. Periglomerular fibrosis occasionally extended into the glomerular tuft resulting in capillary collapse and complete glomerular obsolescence. In some subcapsular glomeruli Bowman's space was markedly dilated. Compensatory hypertrophy of both glomeruli and tubular segments was occasionally observed in cortical segments, but even in these areas widespread interstitial fibrosis was almost constantly present. Obvious hyperplasia of the juxtaglomerular apparatus was occasionally seen in end-stage kidneys. Vascular lesions were usually absent. Slight hypertrophy of the medial layers and segmental intimal fibro-elastosis of the larger arteries were noted only in end-stage kidneys.

The kidney weights of the six patients from whom a nephrectomy or autopsy specimen at the end-stage of the disease was available for morphologic examination, ranged between 45 to 65g. Cysts with a diameter up to 1.5 cm were prominent in five patients at the cortico-medullary border (Fig. 5). They were surrounded by concentric collagen layers and contained a clear fluid. The lining epithelium was cuboidal or flattened, with a transparent cytoplasm. Polypoid structures were occasionally seen along the cyst walls. The calices and the pelvis appeared completely normal.

The kidney surface had a finely granular appearance without localized scarring. Serial sections performed in one case revealed multiple tubular diverticula

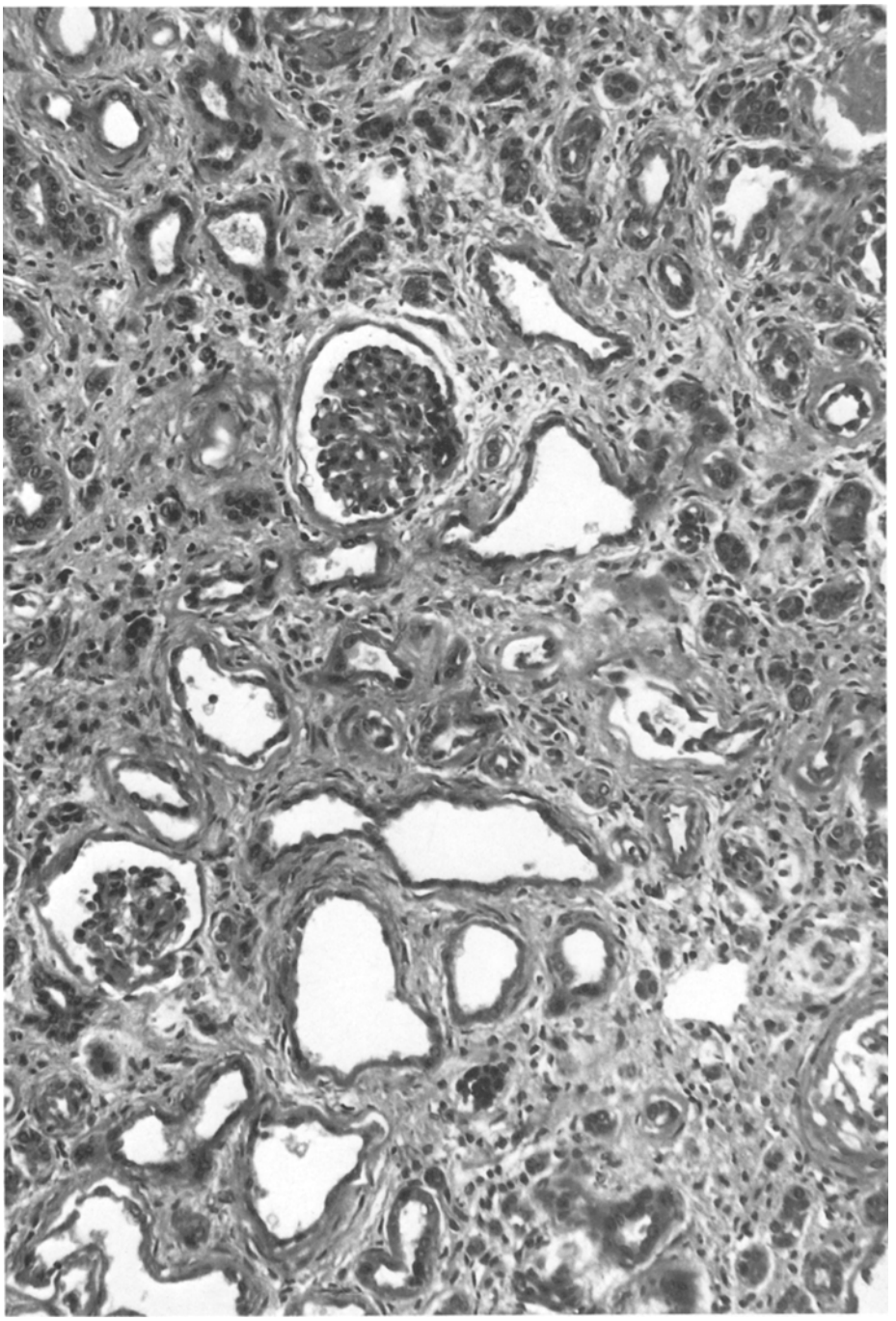

Fig. 3. Juvenile nephronophthisis: diffuse sclerosing tubulo-interstitial nephropathy with marked tubular atrophy and tubular dilatation. Trichrome stain, ×220

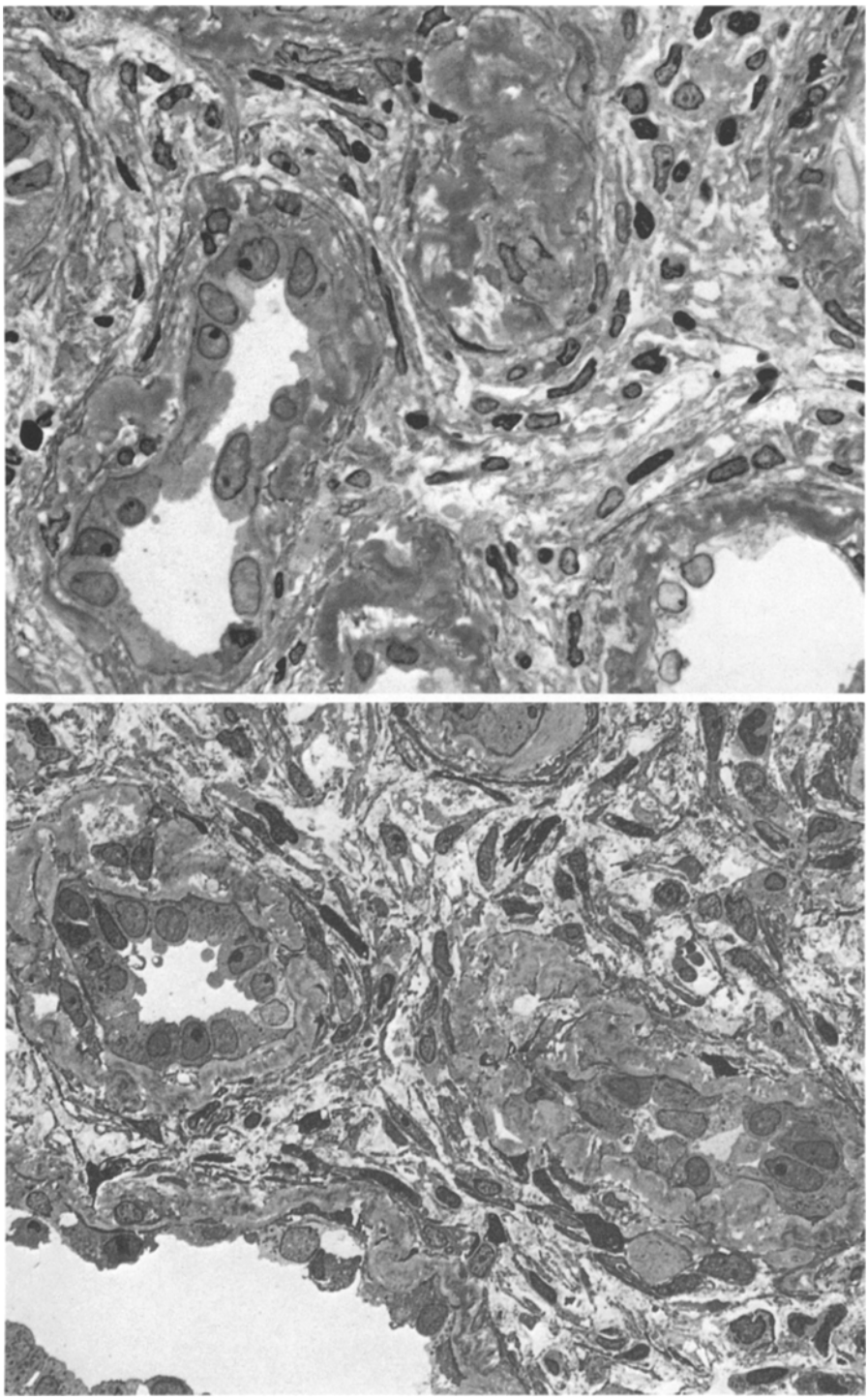

Fig. 4. a Segmental or circumferential thickening and wrinkling of the tubular basement membranes. Concentric peritubular fibrosis. Semithin section, toluidine blue, ×750. **b** Atrophic tubules with multilayered basement membranes and intermembranous lacunae. Note the close contact with peritubular fibroblasts. Semithin section, silver impregnation, ×750

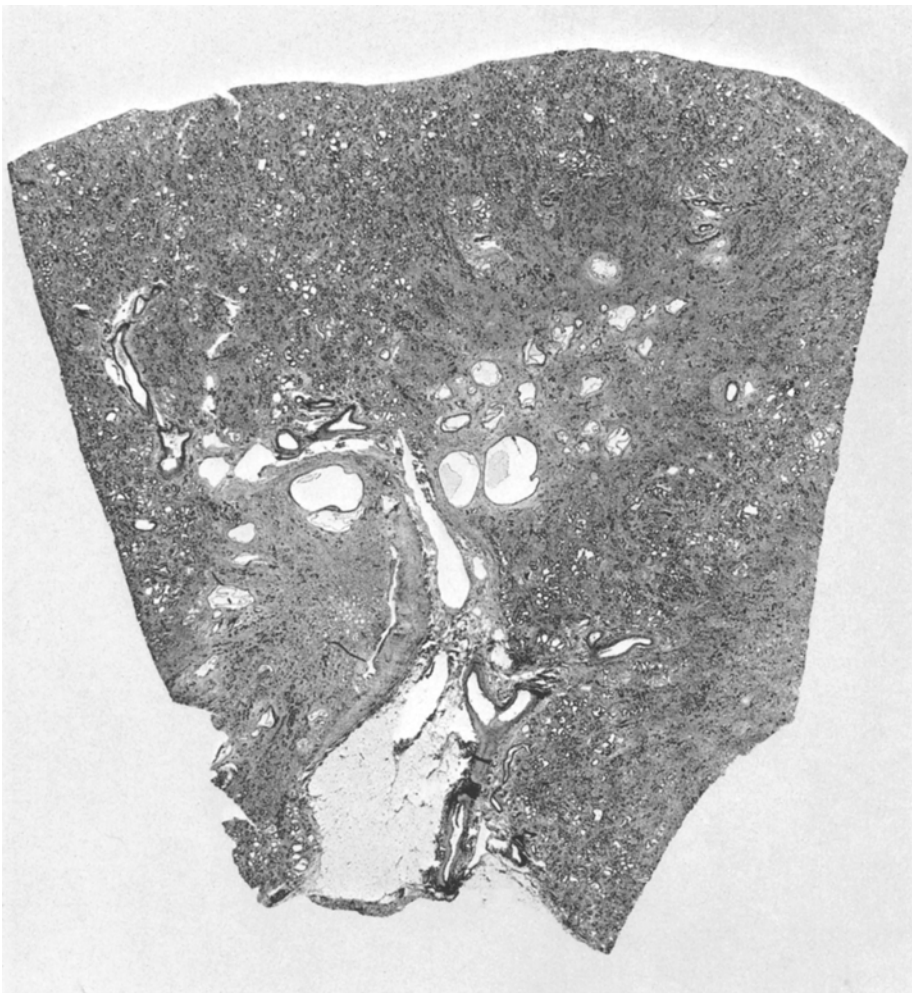

Fig. 5. Nephrectomy specimen: numerous cysts at the cortico-medullary junction. PAS stain, ×7

and free connections between cysts and distal tubular segments. In 5 patients where a post-mortem examination was carried out no liver abnormalities were detected.

Immunofluorescence Microscopy

Significant deposition of immunoglobulins and complement factors suggesting an immune complex disease were never detected. In two biopsies a few glomeruli with intensive periglomerular and partial glomerular tuft sclerosis showed segmental fixation of anti-IgM and anti-C3. The remaining glomeruli were completely negative. Granular and confluent deposits of C9, considered to be non-

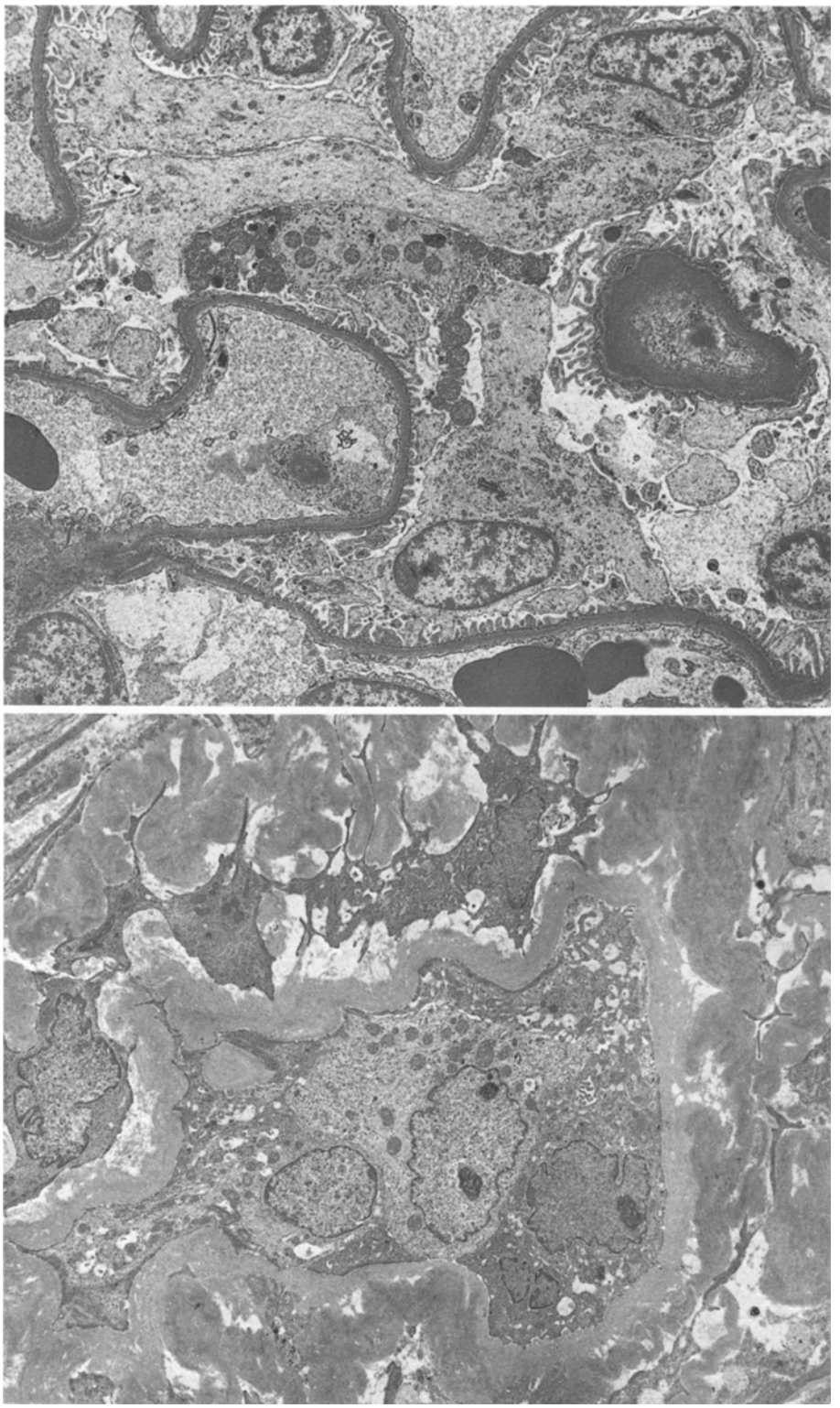

Fig. 6. Thin and regular *glomerular* basement membranes. Electron micrograph, ×4,100

Fig. 7. Multilayered and wrinkled tubular basement membrane with electron lucent areas and dedifferentiated tubular epithelial cells. Electron micrograph, ×3,600

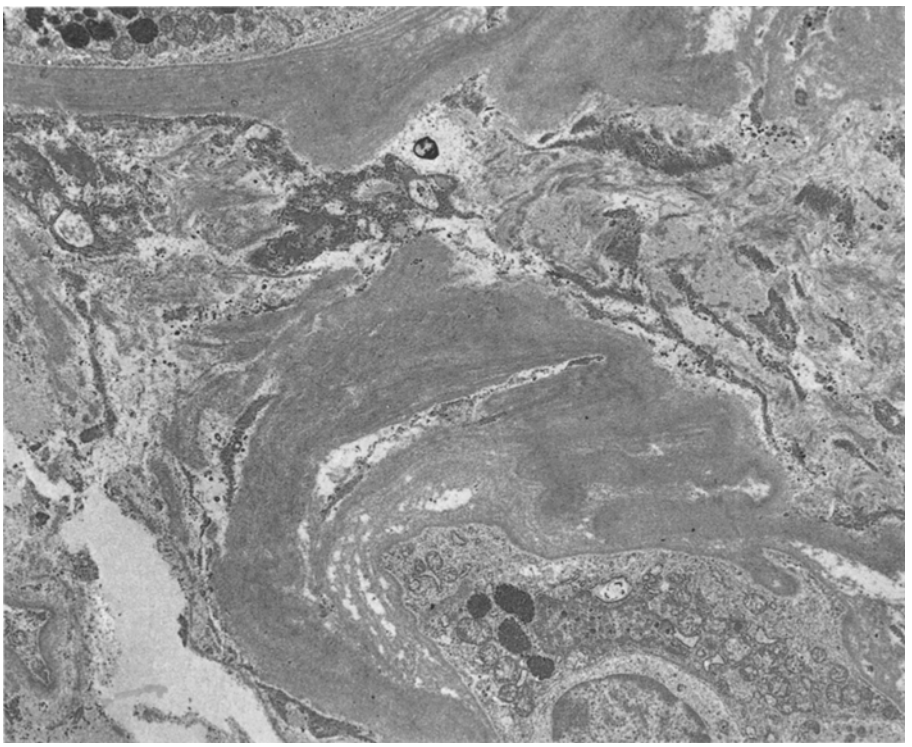

Fig. 8. Segmentally pronounced lamellar thickening of the tubular basement membrane. Note the poorly defined transition between the basement membrane substance and interstitial collagen tissue. Electron micrograph, ×3,700

specific, were observed along the basement membranes of some atrophic tubules in all biopsy specimens examined.

Electron Microscopy

The glomeruli were either normal or showed obsolescence of the collapse type. Glomerular basement membranes were thin and regular, and basement membrane splitting or electron dense deposits were never observed (Fig. 6). No obvious cell proliferation was seen. Endothelial, mesangial and visceral epithelial cells appeared completely normal. Hypertrophied glomeruli exhibited a slight increase in mesangial matrix. Bowman's capsular membrane was frequently thickened, splittered, and surrounded by concentric collagen layers and activated fibroblasts. Parietal epithelial cells were hypertrophied. Collagen fiber bundles were scattered throughout the interstitium and encompassed the tubules as concentric layers. Tubular basement membranes were thickened and reduplicated (Fig. 7). In the early stages of the disease, basement membrane broadening seemed to be segmental or even nodular, whereas in the later stages circumferential membrane thickening became predominant. Thickening was either homogeneous or had a lamellated, annular, ring-like appearance (Fig. 8). The basement

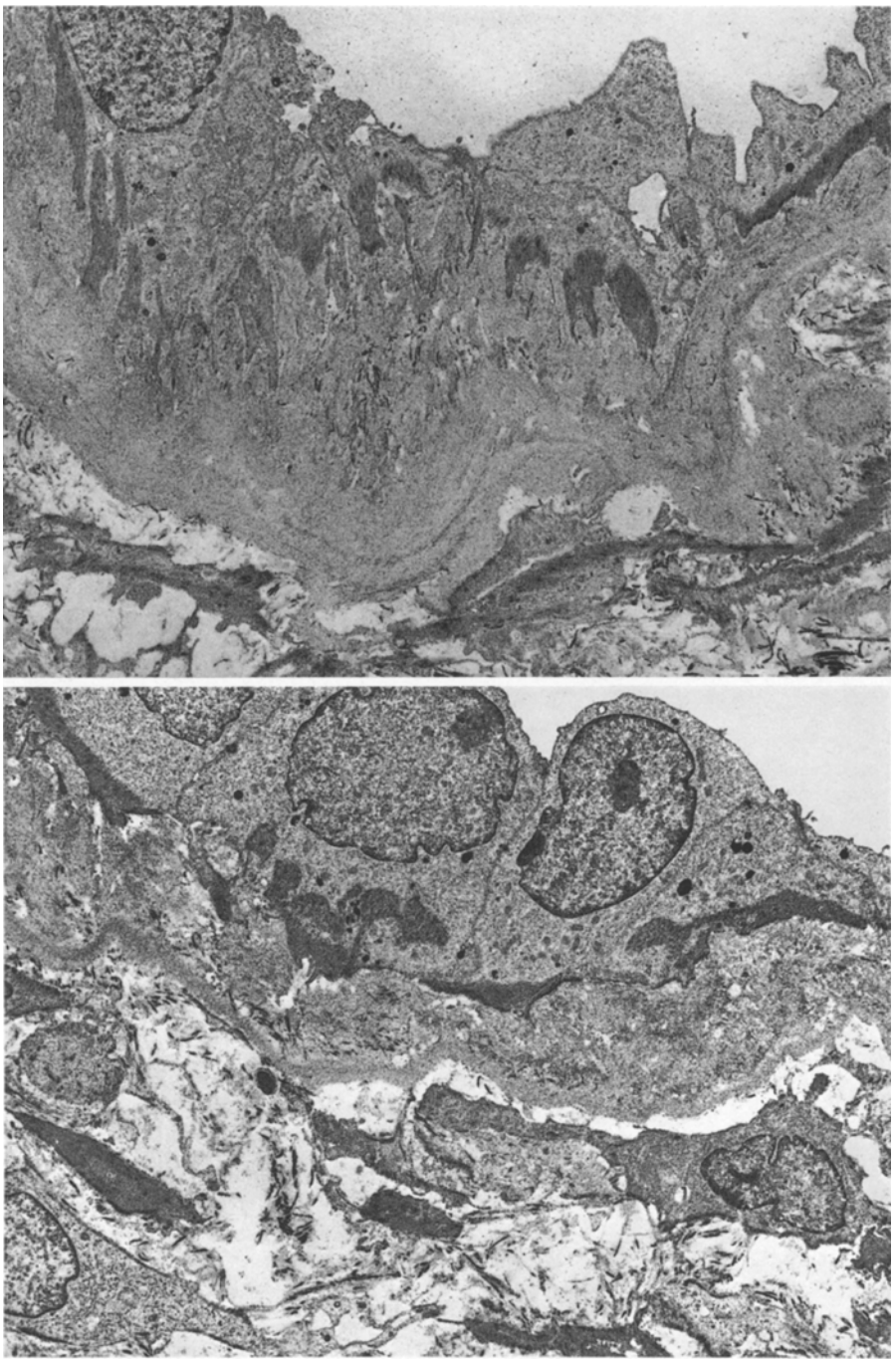

Fig. 9. a Flattening of the tubular epithelial cells. Increase of the tubular basement membrane material with numerous argyrophilic fibrils extending between the tubular epthelial cells. Electron micrograph, silver impregnation, ×3,900. **b** Note the accumulation of a argyrophilic filamentous material at the basal tubular cell membrane. Electron micrograph, silver impregnation, ×3,900

membranes frequently consisted of two or even more membrane layers which were extremely folded. Irregular basement membrane protrusions extended from the luminal side of the membrane between the tubular epithelial cells (Fig. 9). The increased basement membrane substance occasionally exhibited a motheaten appearance and contained numerous microfibrils. Fibroblasts were situated in direct contact with the basement membrane substance around the tubules and in intermembranous lacunae.

At the base of the tubular epithelial cells, we found a marked increase of osmiophilic and argyrophilic microfilaments measuring 50 Å to 100 Å in width. They were condensed into large bundles and were adherent to the basal plasmalemma (Fig. 9b). Tubular epithelial cells displayed degenerative changes of varving degree with an increase in phagolysosomes and residual bodies. However, neither specific mitochondrial changes nor accumulation of foreign material were observed.

Discussion

Today juvenile nephronophthisis is recognized as an important cause of chronic renal failure in the first two decades of life. In our series nephronophthisis accounts for 10% of all pediatric patients with chronic renal failure. This frequency corresponds to the incidence of nephronophthisis reported by the EDTA Registry in the pediatric dialysis population (Schärer et al. 1976). Even higher figures have been observed in French (25%) and English (22%) children (Kleinknecht and Habib 1978; Betts and Forrest-Hay 1973).

Nephronophthisis constitutes a *clinicopathologic entity*. Its clinical onset is insidious; hyposthenuria, growth retardation and anemia are the most important manifestations. There is no history of urinary tract infection and hematuria is absent. Proteinuria is usually slight and of the tubular type (Giselson et al. 1970; Lindstedt and Lindstedt 1973). Distal tubular dysfunction predominates, whereas the proximal tubules are not involved in the early stages of the disease. The clinical course is characterized by a rather slow progressive reduction of glomerular function. The treatment has to be symptomatic. A recurrence of the disease after renal transplantation is not observed (ASC/NIH Renal Transplant Registry 1975; Steele et al. 1980).

Renal biopsy reveals, in the early stage, a focally accentuated, and in later stages, a rather diffuse sclerosing tubulo-interstitial nephropathy with marked tubular atrophy, tortuosity, collapse or dilatation, and peritubular fibrosis. Tubular basement membranes are extremely thickened and multilayered, the increased basement membrane substance contains numerous microfibrils. Fibroblasts are situated in direct contact around the basement membranes and within intermembranous lacunae. Glomeruli are either completely normal or later show severe periglomerular fibrosis and focal collapse obsolescence.

None of these features is specific but the extent of the tubular lesions and the lack of a prominent cellular infiltration is suggestive of nephronophthisis. Microdissection studies (Herdman et al. 1967; Sherman et al. 1971) have shown a heterogeneity of nephron populations with variations in size, the presence of large numbers of diverticula in the loops of Henle and distal tubules as well as cyst formation in the collecting ducts.

In the terminal stages, macroscopic *cysts* are found frequently in the outer medulla or at the cortico-medullary junction of the uniformly and symmetrically contracted kidneys; we observed such changes in 5 out of 6 nephrectomy or autopsy specimens.

The *morphological diagnosis* of nephronophthisis is usually based on the presence of a diffuse sclerosing tubulo-interstitial nephropathy with medullary cysts, and the absence of thyroid-like foci or destructive interstitial inflammation. The demonstration of cysts in biopsy specimens is difficult and usually not possible because material is rarely obtained from the medullary regions of the kidney. In our series, cysts were never observed in specimens from percutaneous or surgical biopsies. On the other hand, it should be borne in mind that cysts can be found in almost all forms of end-stage kidneys, particularly after intermittent hemodialysis (Dunnill et al. 1977). In our experience, however, other forms of contracted kidneys contain cysts which are distributed more irregularly in the cortex *and* the medulla.

It is debatable whether the presence of cysts is an essential criterion for the diagnosis of nephronophthisis. Cysts are absent in approximately a quarter of the cases examined at autopsy (Gardener 1976). In our opinion the combination of the sclerosing tubulo-interstitial nephropathy and the clinical findings described above are characteristic enough for the final diagnosis even in the absence of cysts.

The majority of cysts are thought to develop from the collecting ducts (Zollinger et al. 1980). There is no argument that medullary cysts already exist in the early stages of the disease. They seem to appear de novo and to increase with progression of the disease. In a few families, they were detected in only a small proportion of the patients affected (Sworn and Eisinger 1972; Chipail et al. 1973).

The pathogenesis of cyst formation in nephronophthisis is obscure. There is no evidence that cysts are caused by complete tubular obstruction. In our opinion cyst formation is related to the presence of tubular diverticula, polypoid hyperplasia of the tubular wall, constricting interstitial fibrosis near by the diverticular mouths, and altered compliance of the tubular basement membranes leading to cystic distension of the tubular or diverticular walls.

In recent years, an increasing number of *non-renal abnormalities* have been reported in combination with juvenile nephronophthisis. The best known association is that first described by Senior et al. and Løken et al. in 1961: the combination of nephronophthisis with tapeto-retinal degeneration or retinitis pigmentosa. Subsequently many similar cases were published (Meier and Hess 1965; Herdman et al. 1967; Bois and Royer 1970; Price and Pratt-Johnson 1970; Fontaine et al. 1970; Bennett et al. 1975; André et al. 1975; Fillastre et al. 1976; van Balen und Collenburg 1976; Zollinger et al. 1980). This association was designated as renal-retinal dysplasia or renal-retinal dystrophy (Schimke 1969; Senior 1973; Avasthi et al. 1976).

However, a variety of other ocular changes has also been observed in association with nephronophthisis (see Table 3). An analysis on the incidence of ocular changes in the patients described as having nephronophthisis or medullary cystic disease, excluding those reported as examples of the Senior-Løken syndrome,

Table 4. Juvenile nephronophthisis associated with non-renal manifestations. First descriptions of the various combinations

Author	Mental Retardation	Tapeto-retinal degeneration	Coloboma	Liver fibrosis	Skeletal anomalies	Cerebellar ataxia
Fanconi et al. (1951)	◆					
Senior et al. (1961)		◆				
Løken et al. (1961)	◆	◆				
Boichis et al. (1973)				◆		
Freycon et al. (1977)	◆			◆		
Proesmans et al. (1975)	◆	◆		◆		
Delaney et al. (1978)		◆		◆		
Robins et al. (1976)				◆	◆	
Fontaine et al. (1970)	◆	◆				◆
Mainzer et al. (1970)		◆			◆	◆
Bodaghi and Zaman (1978)	◆	◆		◆	◆	
Dieterich and Straub (1978)	◆		◆	◆		◆
Own observation	◆	◆	◆	◆	◆	◆

or combined with other congenital anomalies, revealed ocular lesions in more than one third of all patients with the recessive type of the disease but only in a single patient with the dominant form (Lennert et al. 1978; Waldherr et al. 1981). This difference supports the theory that two different hereditary varieties exist. A thorough search for ocular changes in patients with nephronophthisis would probably yield an even higher incidence since the early stages of tapeto-retinal degeneration may only be detected by electroretinography.

Further non-renal manifestations include mental retardation, liver fibrosis, skeletal anomalies, and cerebellar ataxia in various combinations. Table 4 gives the references for the first description of these combinations.

Nephronophthisis in association with congenital hepatic fibrosis was first reported by Boichis et al. (1973) in 4 of 7 siblings, and the combination of nephronophthisis, hepatic fibrosis and tapeto-retinal degeneration by Proesmans et al. in 1975.

Congenital hepatic fibrosis occurs as an isolated disease (sporadic or autosomal recessive) and was described in combination with a variety of renal disorders, particularly medullary sponge kidney, polycystic kidneys (Kerr et al. 1961, and 1962; Landing et al. 1980) and nephronophthisis (Boichis et al. 1973; Proesmans et al. 1975; Robins et al. 1976; Freycon et al. 1977; Delaney et al. 1978; Bodaghi and Zaman 1978, 1980; Dieterich and Straub 1978, 1980; Landing et al. 1980). Polycystic kidneys and medullary sponge kidney can usually be differentiated easily from chronic tubulo-interstitial nephropathy of the nephronophthisis type; moreover, the hepatic lesions do not seem to be identical.

Further associated manifestations include skeletal anomalies, particularly

phalangeal cone-shaped epiphyses (Mainzer et al. 1970; Saldino and Mainzer 1971; Chakera 1975; Popović-Rolović et al. 1976; Robins et al. 1976; Bodaghi and Zaman 1978; 1980), and cerebellar ataxia (Mainzer et al. 1970; Fontaine et al. 1970; Saldino and Mainzer 1971; Popović-Rolović et al. 1976; Dieterich and Straub 1978, and 1980; Giedion 1979; Steele et al. 1980).

Three of our patients had liver fibrosis, and in two of these children a concurrence of all previously reported non-renal abnormalities occurred (see Table 4). An increased incidence of red and blonde hair among patients with nephronophthisis (Rayfield and McDonald 1972) cannot be confirmed in our series.

An analysis of the *mode of inheritance* of juvenile nephronophthisis has led to different conclusions in the literature. In most familial cases studied – including our own cases – there is a strong evidence that nephronopthisis is transmitted as an autosomal recessive trait. This is particularly true for those patients with associated extrarenal abnormalities. Consanguinity between parents reported in some families favors this hypothesis (Fanconi et al. 1951; Hooft et al. 1959; von Sydow and Ranström 1962; Meier and Hess 1965; Spicer et al. 1969; Schimke 1969; Price and Pratt-Johnson 1970; Boichis et al. 1973; Habib 1974; Bennett et al. 1975; Fillastre et al. 1976; Bodaghi and Zaman 1978, 1980; Steele et al. 1980). Males and females are affected equally (Gardner 1976). A heterozygous state was assumed to be present in the parents of some patients in whom a urinary concentrating defect was demonstrated (Grüttner and Lenz 1957; Broberger et al. 1960; Mangos et al. 1964; Herdman et al. 1967; Alexander and Campbell 1970; Brouhard et al. 1977). In a few families, however, an autosomal dominant transmission is well documented (Goldman et al. 1966; Gardner et al. 1971; Wrigley et al. 1973; Kliger and Scheer 1976; Avasthi et al. 1976; Coles et al. 1976; Collan et al. 1977), no definite conclusion can be drawn in others (Mangos et al. 1964; Pedreira et al. 1968; Victorin et al. 1970; Giangiacomo et al. 1975). In our opinion the term medullary cystic disease should be applied only to the former group (autosomal dominant) in order to avoid confusion with the autosomal recessive form. A X-linked chromosomal inheritance seems unlikely since there is no sex predilection in either the dominant or recessive group (Chamberlin et al. 1977; Collan et al. 1977).

The concept that juvenile nephronophthisis and medullary cystic disease are related to the form of inheritance is also supported by an age difference in their clinical presentation. Cases with recessive inheritance usually present with their first symptoms during childhood, whereas the dominant pattern has an onset in the third and fourth decade of life. However, the duration of the renal disease does not appear to be different between these two groups (Gardner 1976).

The differences between nephronophthisis and medullary cystic disease with respect to the age at onset, the modes of inheritance and the frequency of associated disorders might support the concept of two completely different disorders. Genetic heterogeneity, however, does not necessarily imply the existence of two distinct entities.

From our study and the results reported in the literature, we believe that juvenile nephronophthisis is part of a larger clinico-pathologic entity which may be termed the "*nephronophthisis complex*" (Table 5). This includes juvenile

Table 5. Classification of the nephronopthisis complex

The nephronophthisis complex
A. Juvenile nephronophthisis (children or adolescents)
Inconstant association with *non-renal* disorders (eyes, liver, skeleton, cerebellum)
1. Familial: autosomal recessive
2. Sporadic
B. Medullary cystic disease (adults)
1. Familial: autosomal dominant
2. Sporadic

nephronophthisis which occurs mainly in children and adolescents. It is frequently associated with extrarenal manifestations, particularly ocular changes, and may be subdivided in an autosomal recessive and a sporadic form. The combination with non-renal abnormalities reflects a variable genetic expression but should not lead to the separation of different syndromes. The other well-defined disorder, termed medullary cystic disease, occurs mainly in adults as a familial or sporadic disease. In contrast to juvenile nephronophthisis, familial cases exhibit an autosomal dominant mode of inheritance. Extrarenal manifestations are generally not observed. The term "nephronophthisiscomplex" for the whole entity is preferable since medullary cysts are not an absolutely constant "hallmark", and have to be considered as secondary phenomena during progression of the disease.

The *pathogenesis* of nephronophthisis is unknown. Fanconi et al. (1951) discussed a "constitutional inferiority of the renal tissue" with tubular destruction and secondary sclerosis. Other authors suggested the possibility of a nephrotoxic substance which leads to early tubular dysfunction and progressive renal damage (Mongeau and Worthen 1977). This hypothesis is favored by the well-known similarity between nephronophthisis and Balkan nephropathy. The latter is thought to be an environmental disease and caused by an as yet unidentified exogenous toxin (Hall and Dammin 1978). The nephrotoxic substance in nephronophthisis could accumulate on the basis of an unknown enzyme deficiency (Senior et al. 1961; 1973; Herdman et al. 1967; Mongeau and Worthen 1967; Fillastre et al. 1976; Chamberlain et al. 1977). There is, however, no evidence for a circulating nephrotoxic or environmental agent, and it should be stressed that nephronophthisis does not recur in transplanted kidneys. A primary immunological disorder is unlikely since immunohistology is negative or non-specific, and prominent interstitial infiltration of immunocompetent cells is lacking. Finally, a structural abnormality of the cell membrane per se with secondary alterations in tubular transport is discussed (Schimke 1969).

The morphological features of nephronophthisis favor the hypothesis of a disturbance of basement membrane metabolism. Tubular basement membranes are multilayered, the basement substance is increased and contains numerous argyrophilic fibrils. Fibroblasts are concentrically arranged around atrophic tubules. The basement membrane changes are accompanied by a loss of tubular differentiation and an accumulation of cytoskeletal, actin-containing microfilaments (Zimmermann and Boseck 1975; Zollinger et al. 1980) at the basal tubular

cell membrane. The increased deposition of basement membrane material has to be interpreted as the result of an imbalance of the relative rates of synthesis and degradation of basement membrane substance. Our results, however, cannot answer the question whether the disturbance of basement membrane production represents the primary event in nephronophthisis, i.e. whether there is a enzymatic defect in basement membrane metabolism ("tubular Alport's syndrome"?), or whether the morphological features are only secondary phenomena of an unknown mechanism leading to epithelial injury and deposition of excessive amounts of basement membrane material. Further studies should be concentrated on the analysis of the major basement components Type IV collagen and laminin to investigate whether there is a qualitative defect in one of these components, or a quantitative difference in the tubular basement membrane composition.

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