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Progressive and nonprogressive hereditary chronic nephritis

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Progressive and nonprogressive hereditary chronic nephritis. Two groups of patients had hereditary chronic nephritis (HCN). The first group included six patients: microscopic hematuria was found in all six; the nephrotic syndrome developed in 3 patients and renal failure in 2. Neural hearing defect was detected in 2 patients. Precise genetic data showed that the deleterious gene appeared to have been inherited from women. Electron microscopic examination of renal specimens revealed a characteristic involvement of the glomerular basement membrane (GBM), whose *lamina densa* was distorted. In contrast, in six of the seven patients of the second group, the nephrotic syndrome and renal failure were not noted during the follow-up period. Renal failure was observed in only one patient, a 62-year-old man. The GBM was normal on examination by electron microscopy. The prognostic value of these data is significant. In addition to nerve deafness, abundant proteinuria and GBM ultrastructural lesion indicate progressive nephritis. Moreover, in affected men the prognosis is worse when the condition is inherited through the mother rather than through the father.

Néphropathies chroniques héréditaires évolutives et non évolutives. Deux groupes de malades atteints de néphropathie chronique héréditaire ont été étudiés. Le premier groupe comprend 6 malades: l'hématurie microscopique était constante; un syndrome néphrotique est apparu chez 3 malades, une insuffisance rénale chez 2. Une hypoacousie de perception a été détectée chez 2 malades. Chez les malades où des données génétiques précises ont pu être utilisées, le gène délétère a été transmis par les sujets de sexe féminin. L'examen en microscopie électronique du fragment biopsique rénal a montré une lésion caractéristique de la membrane basale glomérulaire (MBG) dont la *lamina densa* est désorganisée. Au contraire, chez 6 malades du deuxième groupe, un syndrome néphrotique et une insuffisance rénale n'ont jamais été notés, tout au moins dans les limites du recul actuel. Seul un malade âgé de 62 ans a une insuffisance rénale. La MBG était normale en microscopie électronique. La signification pronostique de ces données a été analysée. En plus de la surdité de perception, la présence d'une protéinurie abondante et de la lésion ultrastructurale caractéristique de la MBG fait craindre une néphropathie évolutive. En outre chez les sujets atteints de sexe masculin, la transmission par la mère a une valeur pronostique péjorative par rapport à la transmission par le père.

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Of the several forms of hereditary chronic nephritis (HCN) which have thus far been described [1], at least two have been associated with clinical prognoses that differ greatly. In families with Alport's syndrome, in which hereditary nephritis is associated with nerve deafness and, occasionally, with eye abnormalities, the clinical course of the underlying nephritis is progressive, often leading to uremia, particularly in male patients who are deaf [1]. In contrast, in patients with "familial benign hematuria" [2, 3], perceptive deafness and renal failure are never seen. Obviously, however, such general statements on a clear-cut prognostic distinction between the two forms are oversimplified, at least to some extent. For example, nondeaf patients belonging to families with Alport's syndrome may exhibit a poor renal prognosis. Similarly, in some kindreds, with hereditary nephropathy and no nerve deafness, progressive renal disease has been documented [1, 4]. Conversely, Chazan et al [5] recently studied a family whose members exhibited nephritis and nerve deafness in association with a benign clinical course, even in the male patients. Furthermore, the renal prognosis has been difficult to assess in female members of families with Alport's syndrome. Affected females usually have a normal lifespan, and deterioration of renal function does not occur. However, on occasion, both deaf and nondeaf female patients have developed renal failure rapidly and unpredictably [6, 7].

The present study focuses attention on the prognostic value of certain clinical, histopathological and genetic data in 13 patients from 13 families with HCN. The results indicate that, in addition to deafness, the presence of abundant proteinuria and ultrastructural changes in the glomerular basement membrane (GBM) are suggestive that renal disease will be progressive. Moreover, the inheritance of nephritis from affected or asymptomatic women leads to a worse prognosis than does inheritance from men.

Material and Methods

Thirteen patients from 13 families with hereditary chronic nephritis were studied. A renal biopsy specimen was obtained from each patient and examined by light and electron microscopy as previously described [8]. For light microscopy renal tissue was fixed in Dubosq-Brasil solution and then embedded in paraffin. Sections were stained with a trichrome stain (Masson), hematoxylin-eosin, periodic acid-Schiff and silver impregnation by Wilder's technique. Blocks for electron microscopy were fixed in 1 per cent osmic acid in 0.1 M phosphate buffer or in 3 per cent glutaraldehyde in 0.1 M phosphate buffer, then post-fixed in 1 per cent osmium tetroxide and embedded in epoxy resin (Epon 812). Thin sections were stained with either uranyl acetate or uranyl acetate followed by lead hydroxide. Periodic acid-silver methenamine stains were systemically performed for light and electron microscopic studies. Grids were examined with an electron microscope (Philips EM 200). For immunohistochemical study fluorescein-labeled goat antisera to human IgA, IgM, IgG and β1C globulin (Hyland Laboratories) and rabbit antiserum to fibrin (Hyland Laboratories) were used. All renal biopsy specimens, except in the case of patient 5, contained five or more glomeruli on examination with light microscopy. In patients of group 2 (see following) 12 to 45 glomeruli from each specimen were examined by light microscopy. An average of 4 to 5 glomeruli on each specimen was studied by electron microscopy.

Urinalysis and renal function tests were performed, and results were expressed as proposed by Hamburger et al [9]. Urinary protein concentrations were determined by the biuret method. The amount of urinary protein excretion was considered to be abnormal when it exceeded 0.04 mg/min. Urinary cell counts were considered to be within normal limits when less than 5,000 erythrocytes and 5,000 leucocytes were excreted each minute. The endogenous creatinine clearance was calculated by the standard formula and corrected for body surface area.

Nonproband subjects were considered to be affected if they had persistent proteinuria or microscopic hematuria, or both. Most of the affected subjects (except in family 12) were studied in our own clinic. Chronic renal failure was detected in two patients. The determination that death was due to renal failure was based on information obtained from either the hospital records or family physicians. A small number of family members who were not affected by the condition were also examined in our clinic.

Statistical significance was determined with the use of Student's t test or the χ^2 test.

Results

Patients were separated into two groups according to the results of histopathological examinations. In group 1 a characteristic ultrastructural lesion of the GBM was demonstrated by electron microscopy [8]. Light and electron microscopy revealed the presence of normal GBM in group 2 (see following).

Clinical data. The six patients in group 1 (Table 1) included three females and three males. Nephritis was discovered when these individuals were between the ages of 2 and 11 years. The first detectable laboratory abnormality

Table 1. Clinical data in patients of group 1

Patient, Sex	Age at discovery of nephritis	Gross hematuria	Clinical data and laboratory values at the time of renal biopsy								Clinical course after renal biopsy				
			Age	NHL[a]	Ocular abnormalities	Proteinuria	Microscopic hematuria	Creatinine clearance	Serum albumin	Hypertension	Nephrotic syndrome	Hypertension	Renal failure	Hemodialysis	Present age
	years		*years*			*mg/min*	*RBC/min*	*ml/min/1.73 m²*	*g/100 ml*						*years*
1, F	3	0	21	0	0	1.0	58,000	117	2.7	0	0	0	0		22
2, M	10	0	14	0	0	1.0	615,000	110	4.2	0	+ [18][b]	0	0		18
3, M	2	+	12	0	0	1.5	2,500,000	92	3.8	0	+	+	+		21
			19			3.0	560,000	[c]	2.8	0		[21][b]	[21][b]		
4, M	4	+	8			0.04	494,000	[c]		0	+	0	+	+	16
			15	+	0	3.0	765,000	82	2.3	0				[16][b]	
5, F	Childhood	0	22	0	0	0.6	266,000	135	3.8	0	0	0	0		23
6, F	6	+	18	+	Anterior lenticonus	2.6	324,000	93	3.2	0					18

[a] NHL: neural hearing loss.
[b] The age in years at which the symptom was first noted.
[c] Blood urea level below 50 mg/100 ml.

Table 2. Clinical data in patients of group 2

Patient, Sex	Age at discovery of nephritis	Gross hematuria	Clinical data and laboratory values at the time of renal biopsy								Clinical course after renal biopsy				
			Age	NHL[a]	Ocular abnormalities	Proteinuria	Microscopic hematuria	Creatinine clearance	Serum albumin	Hypertension	Nephrotic syndrome	Hypertension	Chronic renal failure	Hemodialysis	Present age
	years		*years*			*mg/min*	*RBC/min*	*ml/min/1.73 m²*	*g/100 ml*						*years*
7, M	50	0	62	0	0	0–0.2	15,000	34	4.6	+					62
8, F	4	0	11	0	0	0.06	84,000	125	3.4	0	0	0	0		13
9, F	13	+	20	0	Lens opacities	0.06	800,000	108	4.0	0	0	0	0		22
10, F	11	0	25	0	0	0.1	72,000	110	3.3	0	0	0	0		27
11, F	8	0	9	0	0	0–0.1	860,000	110	3.9	0	0	0	0		14
12, F	2	0	17	0	0	0–0.03	450,000	136	3.6	0	0	0	0		21
13, F	4	+	9	0	0	0.08–0.7	1,400,000	130		0	0	0	0		15

[a] NHL: neural hearing loss.

was proteinuria or hematuria, or both. Recurrent gross hematuria was noted in three patients. Group 1 patients ranged in age from 8 to 22 years at the time of the first renal biopsy. Abnormal amounts of urinary protein excretion were detected in all patients, ranging from 0.6 to 3.0 mg/min. In patient 4 protein excretion was only at the upper limits of normal (0.04 mg/min) at the time of the first renal biopsy. Microscopic hematuria was present in all patients. The presence of the nephrotic syndrome was established by the coexistence of proteinuria (>2.5 mg/min), hypoproteinemia (<6.0 g/100 ml) and hypoalbuminemia (<3.0 g/100 ml) [10]. When so defined, the syndrome was present in two patients at the time of a second renal biopsy (patients 3 and 4). It developed secondarily in patient 2. Abundant proteinuria and a low serum albumin concentration alone were measured in patients 1 and 6.

Renal function was normal at the time of renal biopsy in all group 1 patients except patient 4, in whom a slight decrease in creatinine clearance was detected at the time of the second biopsy. Renal failure developed subsequently in one patient (Table 1); it rapidly necessitated the institution of repetitive hemodialysis in patient 4. Hypertension and renal failure were detected simultaneously in patient 3. Patients in group 1 presently range in age from 16 to 23 years (mean age, 19.7 years).

Neural hearing loss was detected in two patients from group 1 (one male and one female). Slit-lamp examination revealed bilateral anterior lenticonus in one female (patient 6).

Seven patients, six females and one male, were included in group 2 (Table 2). No patient was related to other group 2 patients or to patients in group 1. The first manifestations of renal disease appeared in the patients when they were between 2 and 52 years of age. Gross hematuria was found in three patients. Renal biopsy was performed when patients were between 9 and 62 years of age. At that time significant proteinuria was absent (patient 12), intermittent (patients 7 and 11) or slight (from 0.06 to 0.7 mg/min). Microscopic hematuria was found in all patients. The nephrotic syndrome was not noted in any of the patients in group 2 and did not develop later. Renal clearance was reduced and moderate hypertension was present in patient 7; in patients 8 through 13, renal function remained unchanged in following years. These patients presently range in age from 14 to 62 years (mean age, 24.9 years). Follow-up after renal biopsy ranged from zero to ten years.

The results of audiometric testing were normal in all patients. Nonspecific lens opacities were seen in patient 9.

Family data. Group 1 included patients from six unrelated families (Fig. 1). Consanguinity was known in one family. Nerve deafness was detected in at least one member of each family except for family 3. However, audiometric testing was not performed on any members of this family

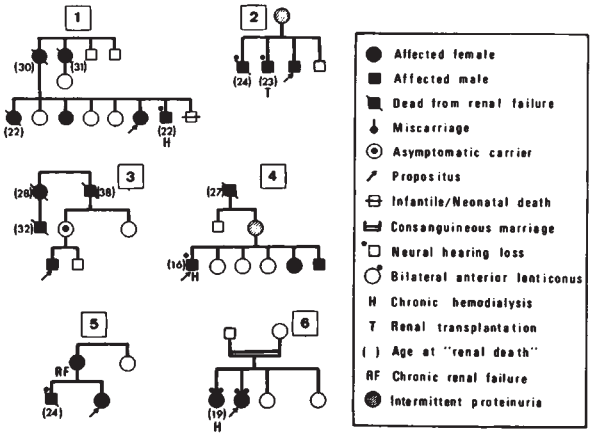

Fig. 1. *Family pedigrees of group 1.*

other than the proband. The probands inherited the deleterious gene from five affected mothers (1–5); the carrier was unknown in family 6.

In addition to the one proband who is presently receiving intermittent hemodialysis (patient 4), 12 relatives had progressive nephritis leading to terminal renal failure (five females, seven males). Of these 12 relatives, one man underwent renal transplantation at 23 years of age (family 2), and one woman (family 6) and one man (family 1) were treated with intermittent hemodialysis from the ages of 19 and 22 years, respectively. Mean age at "renal death" was 26.0 years for women and 25.2 years for men. In addition to probands, inheritance of the gene was determined in three relatives with progressive nephritis (families 1, 3 and 5); in all three the carrier was an affected woman. In two cases (families 1 and 3) the affected women had died of renal failure at 30 and 28 years of age, respectively. In family 5 the female carrier is presently 57 years old and has hypertension and moderate renal failure.

It is striking that the deleterious gene in group 1 families was never known to have been inherited from men. Two severely affected men (in families 3 and 4) had four children, including one male (present age, 40 years); none of the offspring has progressive nephritis.

Group 2 comprises seven families (Fig. 2). Consanguinity was known to be present in family 8. Audiometric testing was performed only on one nonproband subject, and the findings were normal. The seven probands inherited the deleterious gene from three affected women (in patients 7 through 9), from one asymptomatic female carrier (in patient 11) and from three severely affected men (in patients 10, 12 and 13).

In the seven kindreds of group 2, 11 relatives died of renal failure; nine were male ascendants of the probands, one was a female ascendant and one was a male sibling (family 7). Mean age at death was 37.4 years (group 1 versus 2, $P<0.01$). The carrier parent in three of these 11 patients could be determined (families 7, 9 and 12); in all, the carrier was an affected or asymptomatic woman.

In summary, the fact that probands of group 2 inherited the gene from either sex should be stressed. Despite the apparently benign or slowly progressive course of nephritis in probands of group 2, death from renal failure occurred frequently, particularly in male ascendants. When family data were available, they revealed that the deleterious gene in these severely affected patients was inherited from a woman, as in patients of group 1.

Histopathological data (Table 3). In group 1, eight renal biopsy specimens were studied by light and electron microscopy. Two individuals (patients 3 and 4) each had two renal biopsies at a seven-year interval. Histological findings in the first four patients have been reported previously [8].

Kidney structure was nearly normal on examination with light microscopy in five biopsies (patients 1, 2, and 3 — first biopsy; and 5). Mild or moderate mesangial stalk enlargement was noted in glomeruli of all biopsy specimens except in patients 2 and 5; it was associated with minimal or mild mesangial cell proliferation in patient 3 (first biopsy). Immunofluorescence studies revealed no deposits of immunoglobulin or β_1C globulin along the glomerular capillaries in patients 2 and 5. Small foci of interstitial fibrosis and tubular atrophy were found in patients 1 and 3 (first biopsy). Sparse numbers of interstitial foam cells were noted in all biopsies, except in patients 3 (first biopsy), 4 (first biopsy) and 5; foam cells were abundant in the biopsy specimen of patient 1.

Interstitial fibrosis was the most prominent feature in three biopsy specimens (patients 3, second biopsy; 4, second biopsy; and 6). Numerous clusters of foam cells were found in all but one specimen (patient 6). Glomerular involvement was less severe than that of the interstitium. Moderate enlargement of the mesangial stalk and focal thickening of the capillary walls were noted on all specimens. Segmental proliferative changes were also seen in all specimens (Fig. 3). No immunoglobulin or β_1C globulin deposits were detected by immunofluorescence in glomeruli of patients 3 (second biopsy), 4 (second biopsy) and 6.

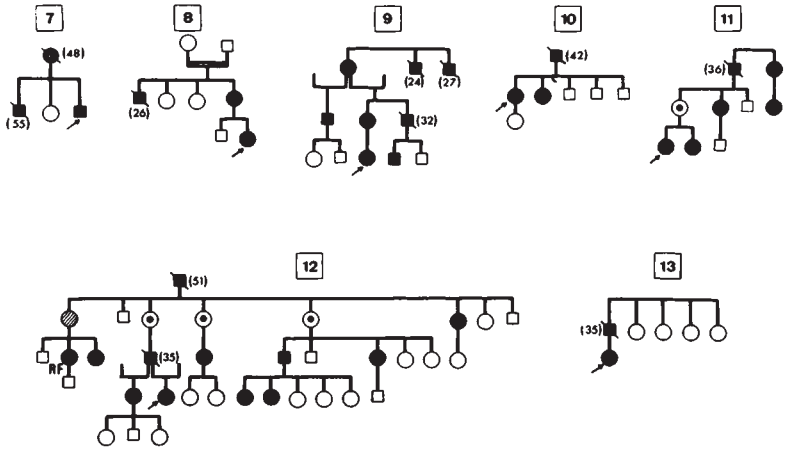

Fig. 2. *Family pedigrees of group 2.*

Table 3. Pertinent histopathological data [a]

Patient no.	Glomeruli [b] no.	Fibrotic glomeruli no.	Segmental proliferative glomerular lesions	Mesangial stalk enlargement	GBM thickening on LM	IH[c]	EM[d]	Focal interstitial fibrosis	Diffuse interstitial fibrosis	Foam cells
1	10	2	0	+	+	ND	2	+		++
2	5	0	0	0	0	Negative	1	0	0	+
3	20	1	0	+	0	ND	1	+		0
	9	3	++	++	+	Negative	2		++	++
4	40	0	0	+	0	ND	1	0	0	0
	8	0	++	++	+	Negative	3		++	+
5	3	0	0	0	0	Negative	1	0	0	0
6	12	4	+	+	+	Negative	3	++		0
7	12	7	0	±	0	Negative	0		++	0
8	45	0	0	0	0	Negative	0	0	0	0
9	40	0	0	0	0	Negative	0	0	0	0
10	12	1	0	+	0	ND	0	0	0	0
11	30	3	0	0	0	ND	0	0	0	0
12	20	3	0	0	0	Negative	0	+		+
13	12	0	0	+	0	ND	0	0	0	0

[a] Morphologic changes seen with light microscopy were graded as follows: 0, normal, ±, questionable; +, mild; ++, moderate; and +++, severe.
[b] On specimen examined with light microscopy (LM).
[c] Immunohistopathological (IH) data; ND: not done.
[d] Electron microscopy (EM) data: 1, focal and mild involvement of the glomerular basement membrane (GBM); 2, moderate involvement of large portions of the loop; and 3, extensive involvement of most capillary loops.

A characteristic GBM alteration was documented in all specimens on electron microscopy. The GBM was irregularly thickened, up to four or five times normal size in some patients. The *lamina densa* was distorted (Fig. 4) and transformed into a heterogeneous network of cloudy material and membranoid strands enclosing clear electron-lucent areas (Fig. 5). These areas contained small granules approximately 500 Å in diameter. The GBM ultrastructural lesion was extensive, involving most capillary loops in two biopsies (patient 4, second biopsy, and patient 6); moderate, involving large portions of the loops in two (patients 1 and 3, second biopsy); and focal and mild in five (patients 2; 3, first biopsy, 4, first biopsy; and 5).

In group 2, seven renal biopsy specimens were studied. Immunofluorescence study was performed in four cases (patients 7 through 9 and 12), and the findings were

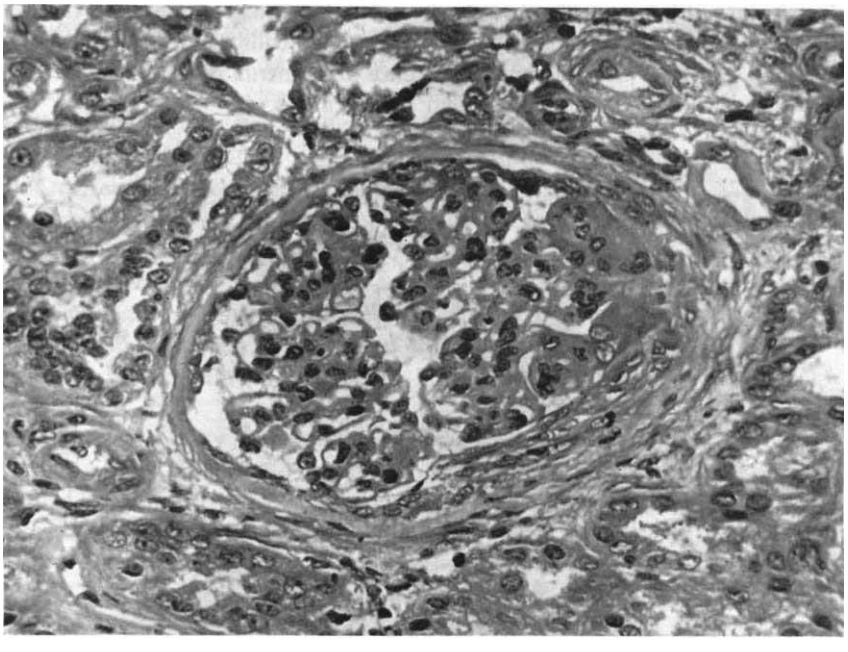

Fig. 3. *Group 2, kidney biopsy (patient 4, second biopsy). Glomerulus with thickened Bowman's capsule.* Segmental lesion with occlusion of capillary loops and epithelial fibrocellular crescent. In the remaining portion of the glomerulus, the mesangial tissue is enlarged and slightly proliferative; capillary loops are irregularly thickened. Note tubular atrophy and periglomerular interstitial fibrosis (trichrome stain, × 652).

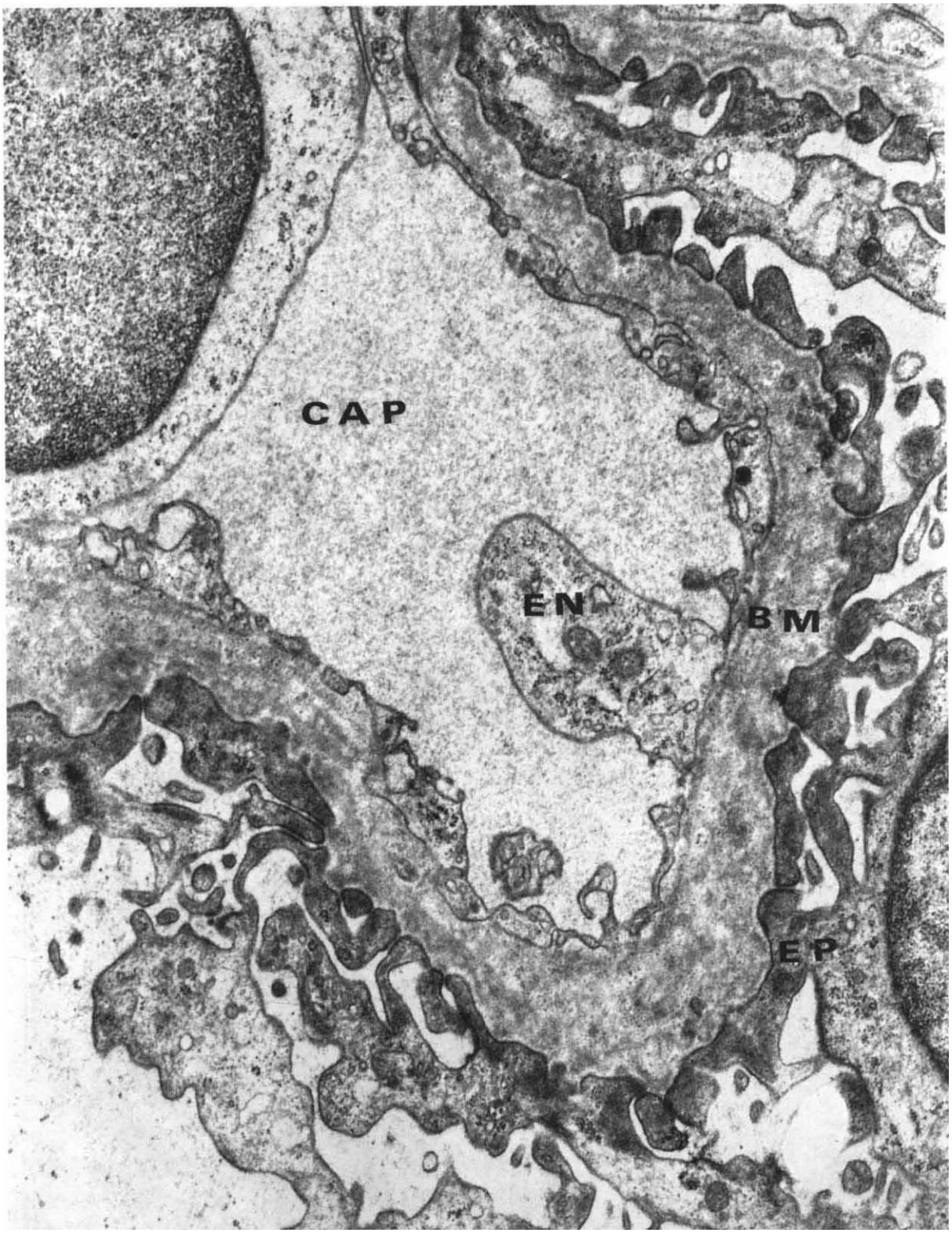

Fig. 4. *Group 1 (patient 6). Abnormal capillary wall.* Basement membrane (BM) is thickened with irregular clarification of lamina densa. Epithelial surface is moderately scallopped with focal widening of foot processes (EP). Endothelial cytoplasm (EN) is slightly ballooned (electron micrograph, × 22,500).

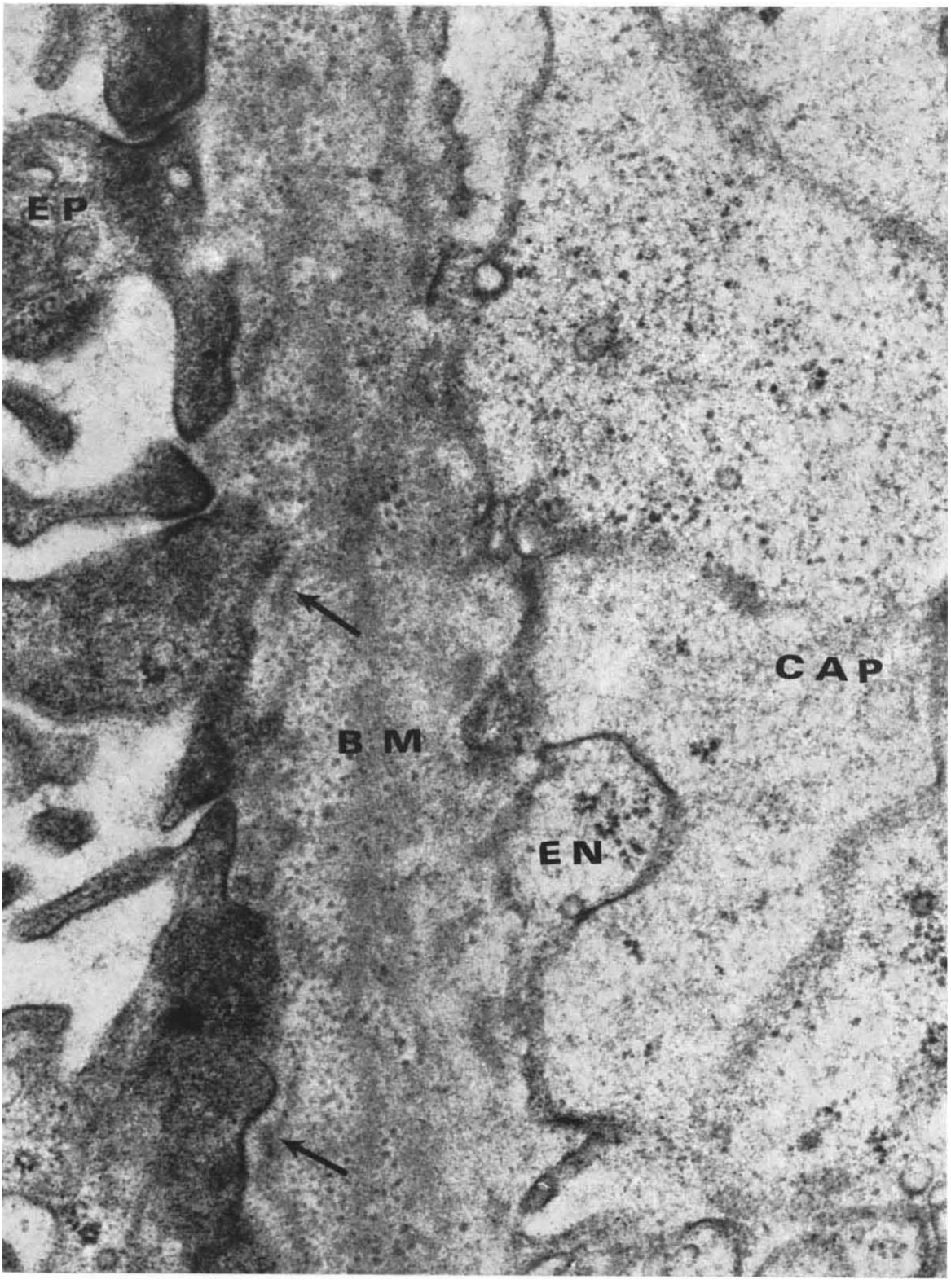

Fig. 5. *Group 1 (patient 6). Basement membrane (BM) lesion.* Lamina densa is split into irregular membranoid strands (*arrow*) enclosing clarified zones punctuated by small round granulations 500 Å in size. These granulations predominate in the outer part of the thickened basement membrane (electron micrograph, × 51,400).

negative in all. The renal parenchyma was strictly normal on examination by light microscopy (Fig. 6) in two cases (patients 8 and 9). Minimal changes were seen on four biopsy specimens. In patient 10, two small adhesions between the glomerular tuft and Bowman's capsule were found; the mesangial stalk and epithelial cells were slightly enlarged. In patients 11 and 12, three obsolescent glomeruli were noted; a few such glomeruli were observed in four patients of group 1. Focal and slight interstitial fibrosis was present in patient 12; three small clusters of interstitial foam cells were found. In patient 13, the glomerular intercapillary spaces were moderately enlarged. In contrast, diffuse interstitial fibrosis was noted in the biopsy specimen of patient 7; no foam cells were seen.

Examination by electron microscopy showed the structure of the analyzed glomeruli to be normal. Most particularly, the GBM exhibited normal thickness and ultrastructure; the *lamina densa* was regular and ribbon-like in appearance (Fig. 7).

Discussion

In 11 of the 13 families that we have studied, at least two members from two different generations have been involved; the diagnosis of HCN would therefore seem to be documented. In two kindreds (families 2 and 6) the genetic criteria for hereditary nephritis were not fulfilled since only two siblings were affected. However, in these two families progressive renal disease was associated with perceptive deafness and, in family 6, with bilateral anterior lenticonus, thus very closely resembling the clinical features of Alport's syndrome [1]. In family 2 the proband's mother had intermittent proteinuria. The exact significance of such a urinary abnormality is questionable. Wide variations in urinary findings among affected females have been noted [11], and intermittent proteinuria has previously been considered to be indicative of renal involvement [12].

The wide spectrum of clinical and laboratory manifestations of HCN is well illustrated by the two groups of patients. Persistent microscopic hematuria was a common finding in both groups. However, the manifestations of renal disease were strikingly different. The six female patients of group 2 had a slight or intermittent proteinuria ranging upwards to 0.7 mg/min. Neither renal failure nor the nephrotic syndrome developed within the follow-up period. At present three of the women are over 20 years of age; the mean age of the whole group is only 18.6 years. Such clinical features as these have usually been observed in most of the affected females in families with Alport's syndrome [1]. Whether or not these women will develop uremia late in life cannot be accurately predicted. In contrast, in the three females of group 1, proteinuria ranged from 0.6 to 2.6 mg/min; in two, excessive proteinuria (patient 6) and persistent hypoalbuminemia (patient 1) probably heralded the presence of the nephrotic syndrome. Similarly, all three male patients of group 1 developed a nephrotic syndrome which, in two of them, was associated with the appearance of renal failure between the ages of 15 and 21 years. The present age of the only male without renal failure is 18 years. By contrast, the only man in group 2 is 62 years of age, and he exhibits intermittent proteinuria and chronic renal failure. The latter clinical course is most uncommon in affected men with Alport's syndrome, and it differs sharply from that observed in males of group 1. Renal disease may well progress less rapidly in group 2 patients, slowly leading to uremia in

Fig. 6. *Group 2, kidney biopsy (patient 12). Normal kidney.* Glomerulus, tubules, interstitium and vessels show no alteration (trichrome stain, × 630).

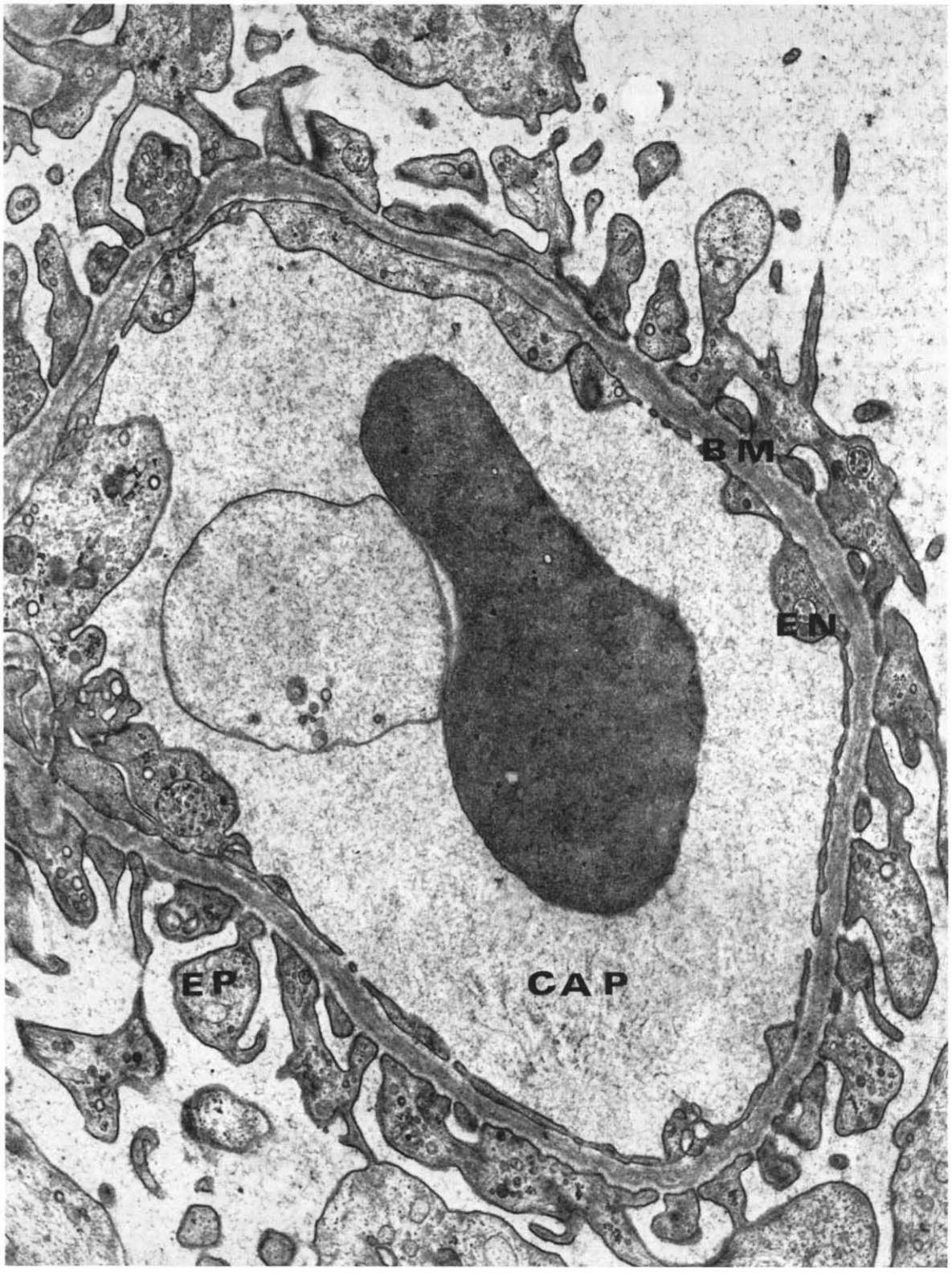

Fig. 7. *Group 2 (patient 12). Normal capillary loop.* Basement membrane (BM) is thin and regular. Epithelial foot processes (EP) and endothelial cytoplasm (EN) are not modified. Capillary lumen is widely patent (CAP) (electron micrograph, × 22,500).

male patients and not progressing at all in most females. Demonstration of the validity of this hypothesis will require the study of a larger number of affected male subjects and longer follow-up of female patients.

In addition to clinical differences, renal histopathological features also differed in the two groups of patients. A characteristic ultrastructural alteration of the GBM [8] was found only in patients of group 1. Such a lesion was present early in the course of renal disease even when the renal parenchyma appeared to be nearly normal on light microscopic examination, as demonstrated on examination of the first biopsy specimen from patient 4, an 8-year-old boy with microscopic hematuria alone. The detection of the ultrastructural change of the GBM is thus suggestive of progressive nephritis, and ultrastructural study may well be of predictive value even when done on renal biopsy specimens from young patients. However, one should remember that the ultrastructural lesion of the GBM is focal at the onset, and that the renal specimen examined by electron microscopy is small in size. Therefore, the absence of the lesion, as in patients of group 2, does not exclude the presence of a segmental, and thus undetected, involvement of the GBM of some glomeruli, and does not preclude its later appearance on subsequent biopsies. Like others [13] we have noted that interstitial changes predominate as the renal disease progresses. Diffuse interstitial fibrosis was present in three cases; renal failure developed in all. In one nonhypertensive boy (patient 4), renal failure progressed rapidly, within a few months, from a slight reduction of creatinine clearance to terminal renal failure necessitating the use of intermittent hemodialysis.

The prognosis of HCN in female patients is unpredictable. Nephritis in many affected women is nonprogressive, marked only by slight proteinuria, often associated with microscopic hematuria, and sometimes exacerbated or first revealed during the course of pregnancy. However, in many kindreds, the nephritis may exhibit a progressive course in a few female subjects. Present data suggest that an ultrastructural analysis of the GBM may be particularly helpful for predicting the renal prognosis in female patients. In some kindreds severe renal involvement has been noted in many affected females [6, 7, 13, 14], as in families 1 and 6 of our series. No genetic explanation has ever been proposed for such an increased incidence.

The diagnostic usefulness of renal histological study in HCN has been questioned recently [5]. It has been stated that histopathological data are nonspecific and that they provide no diagnostic information, especially during the early course of nephritis when renal structure may be normal on examination with light microscopy. Similarly, many of the present renal specimens were nearly normal on light microscopic study. However, the presence of normal renal structure and negative immunofluorescence in a young patient with proteinuria and hematuria should suggest the possibility of hereditary nephritis and audiometric testing, ocular examination and family investigation should be required. In addition to the provision of prognostic information, Hinglais, Grünfeld and Bois [8] have shown that renal biopsies have a diagnostic value provided the specimens are examined with electron microscopy. Besides our patients, the characteristic ultrastructural change of the GBM has been observed in only eight patients with chronic nephritis whose extrarenal symptoms were highly suggestive of Alport's syndrome. Indeed, two of them [8] had nerve deafness but no family history of the syndrome; in one female slit-lamp examination revealed bilateral anterior lenticonus [15, 16]. The remaining six patients consisted of three pairs of siblings, four of whom had a neural hearing defect. The diagnosis of HCN could not be documented in these six individuals, as the siblings alone were affected. Ultrastructural analysis of the GBM may well provide valuable information in these nonclassified cases, in which most of the patients possess a disease that is probably related to Alport's syndrome.

The nephrotic syndrome is generally considered to be rare in HCN [1]. However, Purriel et al [12] stated that the nephrotic syndrome was encountered frequently in their large series of patients with HCN. The occurrence of the nephrotic syndrome has been reported several times [5, 7, 13, 17–23]. In some other cases the probable presence of the nephrotic syndrome seems likely according to the briefly described clinical data [24–26]. The common occurrence of the nephrotic syndrome, as well as the high frequency of persistent microscopic hematuria, strongly suggests that the primary lesion in HCN is glomerular in origin. Such a statement is in accordance with our own data and the results obtained from light microscopic study by Kaufman et al [13]. We found that the abundance of foam cells on renal biopsy specimens was roughly related to the intensity of the ultrastructural glomerular change and to the abundance of proteinuria; foam cells were absent in patients of group 2, except in one case. It is worth recalling that foam cells are not pathognomonic of HCN [1, 11] and that they have been observed in glomerulonephritis, particularly in cases with the nephrotic syndrome and in those whose lesion mainly involves the glomerular capillary wall, e.g., membranous and membrano-proliferative glomerulonephritis [8].

Ocular defects have occasionally been observed in individuals with Alport's syndrome [1], and they are more frequent in male than in female patients [12]. Bilateral anterior lenticonus has been detected rarely and only in male patients [15]. Moreover, bilateral anterior lenticonus without hereditary nephritis has been reported predominately in male subjects, according to the review of Arnott, Crawfurd and Toghill [15]. The occurrence of anterior lenticonus in two sisters in family 6 is, therefore, very uncommon. In three additional female patients with Alport's syndrome, Dr. D. Perrin (personal communication) detected an anterior lenticonus. Anterior lenticonus was demonstrated in four male patients not included in the present series. In all patients, both male and female, an-

terior lenticonus in hereditary nephritis was associated with nerve deafness [15, present series]. Furthermore, Arnott et al [15] have shown that the incidence of nerve deafness is significantly higher in patients with, than in those without, lens defects. As lens abnormalities are more frequent in deaf and male patients, these abnormalities, and more particularly anterior lenticonus, could be indicative of progressive hereditary nephritis.

The mode of inheritance of Alport's syndrome has long been debated [1, 18, 27, 28]. We found no consideration in the literature as to whether or not the sex of the carrier may have some influence on the severity of nephritis in the offspring. It was striking that, in both groups that we studied, patients with progressive nephritis never inherited the deleterious gene from the father. In contrast, patients with nonprogressive nephritis received the gene from either the father or the mother. As our sample was too small to lead to general conclusions, we collected the following data from the literature. Two groups of patients with HCN were selected: A) affected patients who died of renal failure, therefore showing unquestionable evidence of progressive nephritis (115 patients: 100 males and 15 females) [4–6, 12, 14–16, 18, 25–27, 29–37] and B) affected patients with nonprogressive hereditary nephritis, i.e., men alive (or dead) without renal failure at 40 years of age or older, and women alive (or dead) without renal failure at 50 years of age or older (36 patients: nine men and 27 women) [5, 12, 14, 25, 27, 29–31, 33–37] (Table 4). Only data in which precise information was available in the text or pedigrees were selected. In both groups the sex of the carrier has been considered. In group A the gene was inherited from the father in 16 (13.9%) and from the mother in 99 cases (86.1%). In group B the gene was transmitted by men in 11 (30.5%) and by women in 25 cases (69.5%) (χ^2, 5.17; $P<0.05$). If only affected female patients were considered, an identical percentage of them received the gene from the father in either group: five (33.3%) in group A, eight (30.7%) in group B (corrected χ^2 value, 0.03; $P>0.50$).

Table 4. Sex of the carrier in patients with progressive and nonprogressive hereditary nephritis[a]

Affected parent	Affected[b] males	Affected[b] females	Group A: patients with PN[c] M	Group A: patients with PN[c] F	Group B: patients with NPN[c] M	Group B: patients with NPN[c] F
Mother	165 (77.1%)	193 (69.7%)	89	10	6	19
Father	49 (22.9%)	84 (30.3%)	11	5	3	8

[a] Data were collected from the literature as indicated in text.
[b] Data derived from Preus and Fraser [28] (Table 1, lines 5 and 6).
[c] PN = progressive nephritis, NPN = nonprogressive nephritis.

Therefore, transmission from the father or mother in female patients has no prognostic value. Affected male patients of group A received the gene from the father in 11% (11 cases), whereas, males of group B received it from the father in 33.3% of cases (three cases) (corrected χ^2 value, 1.95; $P>0.10$). No valid conclusion may be drawn because of the small number of male offspring of affected men.

Many sources of bias may interfere with the interpretation of such a genetic analysis. For example, male patients usually have very few offspring, and affected males with a benign renal course and affected females with progressive nephritis are scarce. The paucity of affected sons of affected fathers has previously been documented [1, 28]. However, in order to override these objections, data recently published by Preus and Fraser [28] have been considered for comparison. From this study we concluded that of 214 affected males, 22.9% inherited the gene from the father (49 cases) and 77.1% inherited the gene from the mother (165 cases) (Table 4). These values must be compared with those obtained in male patients of group A: in these, the gene was inherited from the father in 11% and from the mother in 89% of cases, figures which are significantly different (χ^2 value, 6.24; $P<0.02$) from the percentages expected by Preus and Fraser [26]. In female patients the percentage of inheritance from the father (30.3%) is not different from the percentage found in groups A and B (33.3 and 29.6%). Therefore, the deficiency of affected sons of affected men does not entirely explain why severely affected sons inherit the gene more frequently from the mother than from the father. Such data may be relevant to those of Preus and Fraser which indicate that there is a relatively low risk that sons of symptomatic fathers will delevop kidney disease. Moreover, Preus and Fraser proposed that an unfavorable intrauterine milieu of the affected mother might increase the gene penetrance into her male offspring [28]. In addition, we conclude that in affected males inheritance from the mother is associated with a worse prognosis than inheritance from the father. Whether genetic or environmental factors are involved remains uncertain.

We cannot conclude whether the patients of groups 1 and 2 represent either the same hereditary nephritis with differing prognoses or two different forms of hereditary nephritis. The absence of nerve deafness in group 2 does not provide decisive support for the latter hypothesis since audiometric testing was not performed in all members of these families. Clinical and genetic data are compatible with the tentative hypothesis that the nephritis of both groups is related to Alport's syndrome. In group 2 the female patients are each known to have had a benign renal course. Histopathological features differed in the two groups of patients we investigated. Unfortunately, in group 2 we had no opportunity to study renal specimens from the parents of probands who had progressive nephritis leading to death from uremia. Such a study would have

contributed conclusively to an assessment of the exact significance of the ultrastructural change of the GBM.

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Addendum

Since submission of this manuscript, the same GBM ultrastructural lesion has been reported in patients with hereditary nephritis by Spear and Slusser (*Am J Pathol* 69:213–220, 1972) and by Churg and Sherman (*Arch Pathol* 95:374, 1973).

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