

Hereditary nephropathy with hematuria (Alport's syndrome)

Summary: Among 82 members and four generations of a French-Canadian family, 14 cases of hereditary nephropathy (Alport's syndrome) were documented. Five additional members of the family had died, probably because of this same illness. Deafness occurred in five family members with nephropathy and in one without renal disease. Ten of 12 affected males died in uremia before they had reached the age of 40 years. One of seven affected females died following a pregnancy. In two surviving patients, special investigations failed to elicit intrinsic tubular defects such as amino-aciduria, renal tubular acidosis, hyperphosphaturia or renal glucosuria. Systemic illness such as abnormal amino-acids in serum, primary hyperoxaluria, diabetes mellitus and infections were also excluded. Immunological defects were not demonstrable and the staining of renal biopsy tissue with fluorescein-labelled anti- β_2 g, anti-IgG and anti-fibrinogen was negative. Renal tissue material of early, advanced and terminal hereditary nephropathy showed both tubular and interstitial, vascular and glomerular lesions. Electronmicroscopy showed marked thickening of tubular and glomerular basement membranes, increase of mesangial tissue and fusion of foot processes but failed to demonstrate "immune deposits." It is postulated therefore that hereditary nephropathy results from an inborn error of metabolism where an as yet unidentified metabolite damages the renal tissue as well as the acoustic nerve, analogous perhaps to the action of certain drugs, e.g. nephro-ototoxic antibiotics.

A. CHIRICOSTA, M.D.,
S. L. JINDAL, M.B., M.R.C.P., F.R.C.P.[C],
J. METUZALS, PH.D. and
B. KOCH, M.D., F.R.C.P.[C],
Ottawa, Ont.

with the technical assistance of
SANDRA ERRINGTON and
V. F. REDMOND

Hereditary nephropathy was first reported by Dickinson¹ in 1875, almost 100 years ago. Since then more than 40 families with this condition have been reported.¹⁻³³ In 1927 Alport² noticed the associated nerve deafness, and his name has since been attached to this disease. Patients with the syndrome present with hematuria and casts; nerve deafness occurs in 30%

of cases. In males the disease is usually progressive, gradually leading to uremia and hypertension, and death occurs in the third or fourth decade. In females it usually pursues a benign course, but clinical exacerbations are common during pregnancy. Cataracts, spherophakia and other ophthalmological complications have been described.^{7,12,14,17,26,34} The condition must be distinguished from other hereditary nephropathies, e.g. those associated with the nail patella syndrome,^{35,36} with Fabry's disease,^{37,38} and with hyperprolinemia.^{41,42} In 1963 Mulrow *et al.*¹⁶ concluded from several large genetic studies that the disease is transmitted as an autosomal dominant with non-random segregation and preferential association of the autosome bearing the gene with the x-chromosome during meiosis.

Material and methods

In the last two years we had occasion in the Ottawa Civic Hospital to study hereditary nephropathy in a French-Canadian family L. comprising 82 members. There was no consanguinity in this family. One branch resides in Washington, D.C., and information on these individuals was kindly furnished by Dr. J. B. D'Albora of Georgetown University.

Fluorescein-labelled antibody staining of tissue specimens was done by the method of Drummond³⁹ and serum complement and immune globulins were measured on immunodiffusion plates.⁴⁰ Amino-acids in serum and urine were determined by column chromatography. *Tissue for electronmicroscopy was fixed within 15 seconds in cold osmium tetroxide prepared with Veronal acetate buffer of pH 7.4. The electronmicroscope was a Phillips 100 B; pictures were taken at 60 kv. All other investigations were carried out using conventional techniques.

Family report

The family tree is shown in Fig. 1. No useful health information was available from 50 of the 82 family members. Thirteen members were said to be free of renal disease. Five members had died of renal disease, but no medical documentation was available

*Technicon automatic amino-acid analyzer.

A. CHIRICOSTA, M.D., Resident in Urology, Ottawa Civic Hospital, Ottawa, Ontario.
S. L. JINDAL, M.B., M.R.C.P., F.R.C.P.[C], Resident in Nephrology, Ottawa Civic Hospital.
J. METUZALS, PH.D., Professor of Histology and Embryology, University of Ottawa.
B. KOCH, M.D., F.R.C.P.[C], Head of Nephrology Unit, Ottawa Civic Hospital.
Reprint requests to: DR. B. KOCH, Nephrology Unit, Ottawa Civic Hospital, Ottawa 3, Ontario.

(Cases 1-3, 6, 12). Of these, four were males and three were under 33 years of age at the time of their death. The only female in that group had a long history of albuminuria and died at the age of 27 years, shortly after her only pregnancy had terminated in an abortion. In 14 members, clinical documentation of nephropathy was available and is listed in Table I. Of the eight males in this group six have died from uremia at a young age, but two females have survived to the age of 63 years (Cases 4 and 5). Proteinuria was common but was not usually associated with the clinical nephrotic syndrome. In Case 14 (the propositus) the amount ranged from 3 to 8 g. per 24 hours. His serum usually looked milky and his total serum lipids were 1940 mg. per 100 ml., almost twice the normal figure. Hematuria was documented in all but three cases.

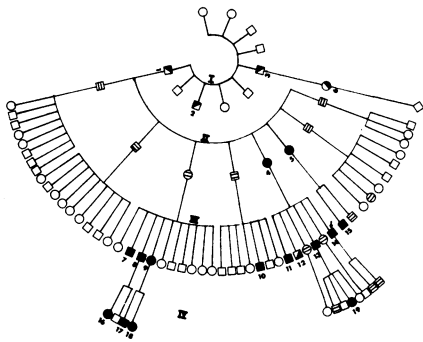


FIG. 1—Family tree of family L. with hereditary nephropathy with hematuria. Figures refer to affected members mentioned in text and subsequent illustrations. Open symbols—no information available; hatched symbols—documented absence of renal disease; half-black symbols—renal disease only documented by history; black symbols—documented renal disease; squares—males; circles—females; diamond—abortion; arrow—propositus.

Pyuria, on the other hand, was less frequent and positive cultures were obtained only in two cases, each following instrumentation. Casts were usually of the heme-granular or red-cell type. Blood pressure and blood urea nitrogen (BUN) rose with the approach of the terminal phase. Cholesterol was often elevated, especially in cases with more pronounced proteinuria. Hyperphosphatemia and hyperuricemia were usually attributable to impaired renal function. High-frequency nerve deafness was documented by audiometry in Case 14 and in another family member who had no evidence of renal involvement. In addition four patients had a history of deafness (including Case 1).

Additional clinical studies

In the propositus, Case 14, and in his niece, Case 19, the following additional tests were performed and will be reported jointly. Karyotyping and examination of leukocytes for Barr bodies were normal for their individual sex. Visual acuity and ophthalmoscopic examination of ocular media and fundi were normal. Throat cultures were negative and serum antistreptolysin O titres were not elevated. Hemoglobin, peripheral leukocyte count, differential leukocyte count, the LE preparation and serum protein electrophoresis were normal. There was no hyperglycemia after a standard oral glucose load. In both, β_1c and serum immune globulins A, G and M were within the normal range with the exception of IgA in Case 19 which was low on three occasions (Table II).

TABLE II
Serum β_1c and immunoglobulin levels in two family members with hereditary nephropathy with hematuria

Serum	β_1c	IgA	IgG	IgM
Normal (mg. per 100 ml.)	145 ± 25	288 ± 121	900 ± 300	80 ± 30
Case 14	151	257	715	70
Case 19	145	68	848	68

Tubular function tests in these two patients are listed in Table III. Serum amino-acids were within the normal range. There was no aminoaciduria, glucosuria, hypercalciuria, hyperphosphaturia or hyperoxaluria. Both patients were able adequately to acidify their urine after a standard oral acid load of ammonium chloride; tubular reabsorption of phosphorus was normal.

Morphological studies

Renal tissue was available in five cases, in three of them by biopsy (Table IV). The original pathological diagnoses were made without a knowledge of the family history and varied somewhat from case to case. Reassess-

TABLE III
Investigations of urine in two family members with hereditary nephropathy with hematuria

Urine	Case 14	Case 19
Glucose	neg.	neg.
Aminoacids	neg.	neg.
Minimum pH*	<4.7	<5.7
Phosphates (mg./24h.)	—	335
Calcium (mg./24h.)	35	248
Oxalates (mg./24h.)	16	3
Tubular reabsorption of phosphate (%)	89	87

*6 to 8 hours after oral ammonium chloride, 0.1 g./kg.

TABLE I
Summary of clinical findings in 14 family members affected by hereditary nephropathy with hematuria

Case No.	Age (years)	Sex	Clinical			Urine					Blood						
			Blood pressure (mm. Hg)	Age at onset of hematuria (years)	Deafness	Protein	RBC HPF	WBC HPF	Casts	Culture	Blood urea nitrogen (mg. per 100 ml.)	Serum creatinine (mg. per 100 ml.)	Creatinine clearance (ml./min.)	Cholesterol (mg. per 100 ml.)	Phosphorus (mg. per 100 ml.)	Uric acid (mg. per 100 ml.)	Albumin (g. per 100 ml.)
4	64	F	140/90	x	x	3+	5	10	+	x	x	x	x	x	x	x	x
5	63	F	x	x	x	1+	5	—	—	x	x	x	x	x	x	x	x
7	†38	M	176/105	8	+***	4+	15	6	—	x	346	x	x	x	14.9	9.3	2.3
8	†38	M	160/100	18	+***	4+	TNTC	30	+	x	344	19.8	x	330	x	7.5	3.1
9	39	F	x	17	x	1+	+	x	+	x	x	x	x	x	x	x	x
10	†20	M	200/140	19	x	4+	x	5	+	+	220*	10.0	x	x	x	x	3.0
11	†20	M	x	x	x	3+	x	2	x	x	60*	x	x	230	8	x	x
13	†25	M	250/150	23	+***	3+	TNTC	5	+	x	302*	19.5	x	x	x	x	1.6
14	26	M	160/110	10	+	4+	TNTC	20	+	—	12	1.7	70	296	4.5	7.2	—
15	†23	M	x	x	x	3+	x	x	x	x	159*	14.8	x	x	x	x	—
16	7	F	100/60	2	x	1+	TNTC	20	+	+	12	0.6	x	x	x	x	4.4
17	4	M	Normal	2	—	1+	TNTC	rare	—	—	24	1.0	135**	145	x	x	3.3
18	2	F	Normal	2	—	x	10	x	—	—	x	x	x	x	x	x	x
19	13	F	112/62	12	—	2+	TNTC	10	+	—	17	0.6	102	216	4.4	4.6	3.8

†Death. TNTC—too numerous to count. +Positive. —Negative. xInformation not available.
*Non-protein nitrogen. **Inulin clearance, per 1.73 m², PAH clearance 482 ml./min./1.73m². ***History of deafness.

TABLE IV
Pathological findings in kidneys of five family members with hereditary nephropathy with hematuria

Case	Source of tissue	Weight (g.)		Foam cells	Original pathological diagnosis
		Rt.	Li.		
8	Autopsy	75	50	+	Membranous glomerulonephritis with hyalinization
10	Autopsy	60	60	0	Chronic glomerulonephritis
14	Biopsy	—	—	+	Chronic glomerulonephritis
19	Biopsy	—	—	0	Early proliferative glomerulonephritis
17*	Biopsy	—	—	+	Familial hematuria, fetal glomeruli

*Correspondence with Dr. J. B. D'Albora, Georgetown University.

ment of these specimens revealed a number of common features and provided a unique opportunity to study successively more advanced stages of the disease.

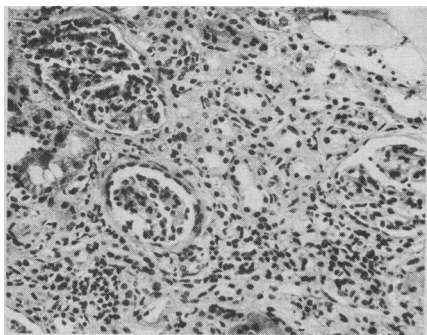


FIG. 2—Case 19. Renal biopsy showing local glomerular hypercellularity, interstitial fibrosis and tubular atrophy. (Hematoxylin, phloxine and saffron, $\times 450$.)

Case 19, a 13-year-old girl, represents an early phase of the disease. She has been admitted to the Ottawa Civic Hospital several times for benign hematuria but is clinically asymptomatic. Her creatinine clearance is 102 ml. per minute. Kidney biopsy showed local glomerular changes affecting a very small proportion of glomeruli and consisting of slight hypercellularity, periglomerular fibrosis and rarely an obliterated glomerulus (Fig.

2). Occasionally red cells were seen in Bowman's space and tubules. In the vicinity of affected glomeruli there was mild interstitial fibrosis and local tubular atrophy.

A more advanced phase is represented by Case 14, the uncle of Case 19. He is a 27-year-old truck driver and is clinically asymptomatic most of the time but has had documented hematuria for the past 18 years. His creatinine clearance is reduced to 70 ml. per minute. Light microscopic changes in this man were more advanced than in Case 19. Some glomeruli showed capsular adhesions and thickening of the capillary wall (Fig. 3a), and others showed proliferation of mesangial cells (Fig. 3b). There were streaks of interstitial fibrosis containing typical foam cells and calcium-like deposits. Some tubules were dilated and contained eosinophilic casts (Fig. 3c) while others, especially those surrounding glomeruli, were atrophic. Both proximal and distal tubules exhibited marked thickening of their basement membrane (Fig. 3a) and there was marked arteriosclerosis. Sections of the biopsy were stained with fluorescein-labelled antibody against β_2 , immune globulin G and fibrinogen. No fluorescence was dem-

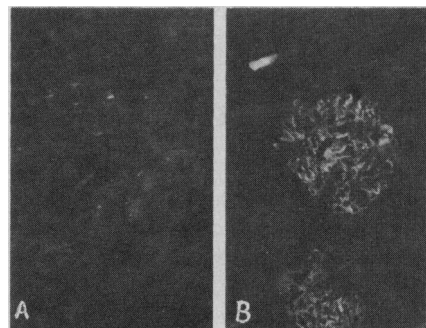


FIG. 4—Case 14. (a) Renal biopsy stained with fluorescein-labelled rabbit anti-human immune globulin G, demonstrating complete absence of fluorescence, compared to (b) a positive specimen from another patient with membranous glomerulonephritis prepared in an identical fashion. (Both $\times 450$.)

onstrable in either case (Fig. 4). Electronmicroscopy in this patient showed marked glomerular changes (Figs. 5a, 5b and 6). Only short stretches of normal basement membrane were left, and these merged into huge irregular masses of basement membrane-like material which in some areas contained coarse granular material. On higher magnification some of these granules had a dense core surrounded by a halo, reminiscent of virus particles. Immune deposits typical of membranous glomerulonephritis were not seen. The capillary tufts contained numerous nuclei but endothelial and mesangial cells could not be differentiated. The capillary lumina were very narrow, if not obliterated, and contained some platelets and polymorphonuclear cells but no red blood cells. Epithelial foot processes were fused, and occasional fibrin deposits and crescents were contained in Bowman's space. The tubular architecture was more intact, but the basement membrane was also markedly thickened and its infoldings were absent.

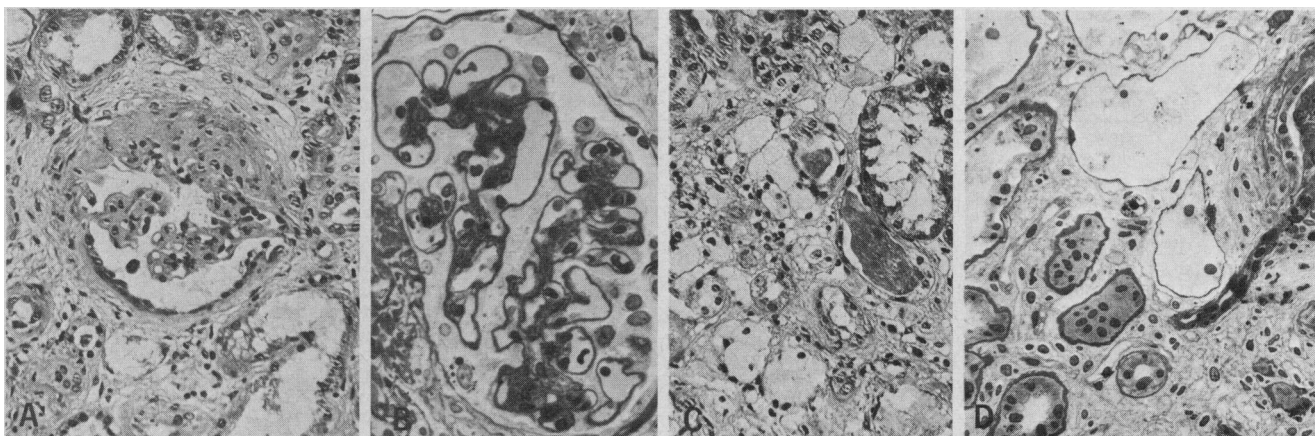
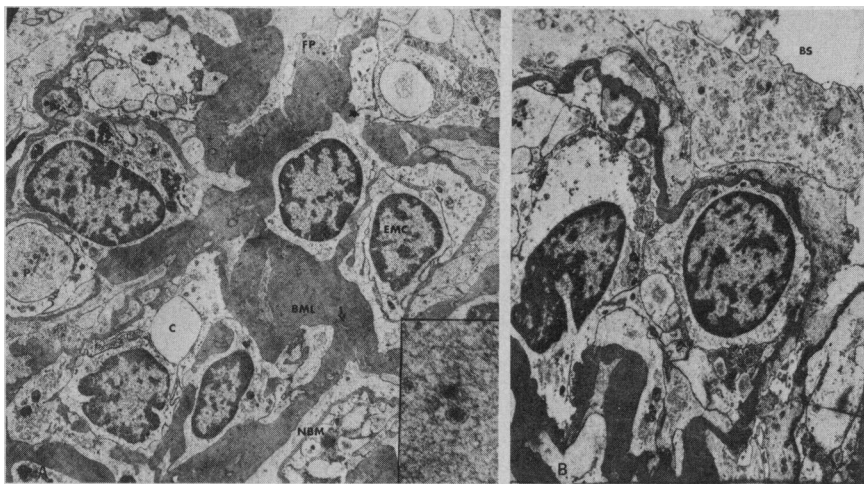


FIG. 3—Case 14. (a) Glomerular adhesion and periglomerular fibrosis; (b) glomerulus showing mesangial proliferation; (c) interstitial foam cells; (d) proximal and distal tubules showing thick basement membrane. (A,C: hematoxylin, phloxine and saffron. B,D: toluidin blue stain of 1μ section. All $\times 450$.)



FIGS. 5a and b—Case 14. Electronmicrograph of renal biopsy. Short stretches of normal basement membrane (NBM) merge into huge masses of basement membrane-like material (BML) containing granules (arrow). Insert shows these to have a virus-like appearance. Endothelial and mesangial cells (EMC) cannot be differentiated. Capillary spaces (C) are nearly obliterated. Foot processes (FP) are fused. BS—Bowman's space. P—platelet. (Approximately $\times 8000$, insert approximately $\times 20,000$.)

The terminal stage of the disease is illustrated by the findings of Cases 8 and 10 which were obtained at autopsy (Figs. 7 and 8). The kidneys were contracted with diffuse histological changes. Scarce and atypical foam cells were demonstrable. Interstitial fibrosis was marked and there were areas of "pseudothyroidization", features that might mislead one to label such findings as chronic pyelonephritis. Occasional calcium deposits were present in the interstitium. The majority of the glomeruli were obliterated and there were severe arteriosclerotic changes. These, as well as the so-called "fetalization" of glomeruli, are said to be more common in hereditary nephropathy.⁵⁹

Discussion

A somewhat confusing terminology has been attached to Alport's syndrome. Hereditary pyelonephritis has at times been used^{7,8,18,25,32} but it is obviously illogical to imagine an inherited infection. Most of the reported cases may well represent secondary infections. With respect to the often abused term "chronic pyelonephritis" there is accumulating evidence that specimens labelled as such do not necessarily indicate an infectious etiology but may rather reflect metabolic disease and are therefore better called chronic interstitial nephropathy.^{43,44}

Considerable advances have recently been made in the study of glomeru-

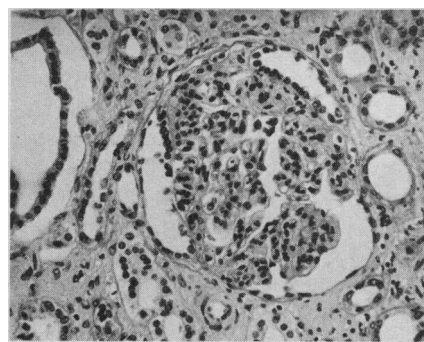


FIG. 7—Case 8. Kidney at autopsy showing advanced interstitial fibrosis and deposition of eosinophilic material in dilated tubules. (Hematoxylin and eosin, $\times 450$.)

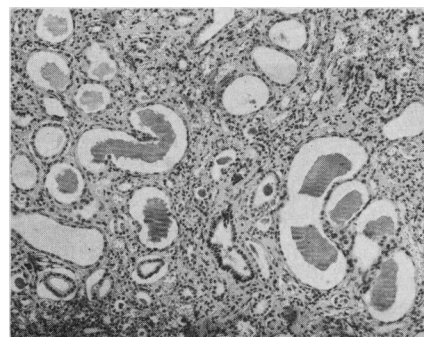


FIG. 8—Case 10. Kidney at autopsy showing "fetalization" of a glomerulus. (Hematoxylin and eosin, $\times 450$.)

lonephritis. These have led to the concept that glomerulonephritis represents an immunoinflammatory disease.^{39,45} Pertinent studies in two affected members of this family included examination of the peripheral blood smears, estimation of serum complement, serum immune globulins and immunofluorescent staining of renal tissue; these were all normal. Electronmicroscopy failed to show immune deposits. Absence of immunofluorescence has been reported by Vernier *et al.*⁴⁶ Corticosteroid and azathioprine treatment have been reported as unsuccessful.^{23,47} It is therefore improbable that inherited susceptibility to infection or to endogenous or exogenous antigenic sensitization causes hereditary nephropathy.

Known causes of non-infectious, non-immunological nephropathy can also be excluded. There was no history of analgesic abuse, sulfonamide treatment or primary gout. Renal tubular defects and hypercalcemia were excluded by clinical studies. In 1966 Krickstein, Gloor and Balogh⁴⁸ conducted a careful morphological study by light microscopy of hereditary nephropathy and concluded that a genetically controlled enzyme defect might be the cause of this disease.

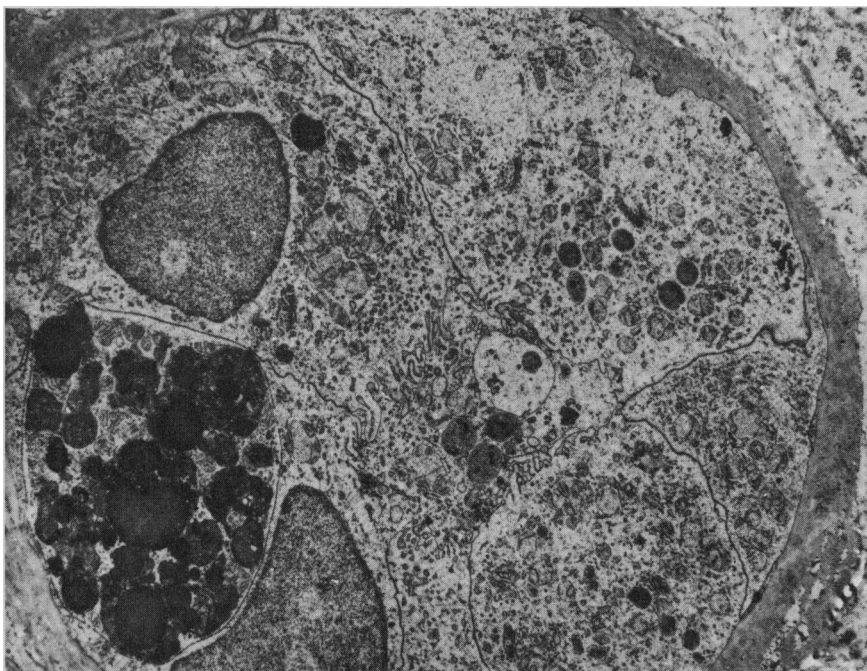


FIG. 6—Case 14. Electronmicrograph of renal biopsy showing a proximal tubule. The basement membrane is thickened and the membrane infoldings are absent. (Approximately $\times 8000$.)

Certainly one can speculate that such an enzyme defect may result in the accumulation of an as yet unidentified metabolite that is toxic both to the kidneys and the acoustic nerve, analogous to the action of certain antibiotics. Hyperprolinemia has been reported in association with hereditary nephropathy and deafness,^{11,31,41,42} but also secondary to renal failure.⁴⁹ It is interesting in this context to note that only very scarce morphological descriptions exist of those nephropathies that are associated with many known inborn errors of metabolism, e.g. tyrosinosis^{50,51} and hyperprolinemia^{41,42} and with administration of otonephrotoxic antibiotics.⁵²⁻⁵⁴ Whalen *et al.*²⁸ originally considered foam cells as diagnostic for hereditary nephropathy but later modified this view.⁵⁵ Krickstein, Gloor and Balogh⁴⁸ suggested that foam cells in a typical distribution have diagnostic significance. Marin and Tyler⁵⁶ demonstrated foam cells in both renal and nervous tissue from a case with hereditary nephritis with polyneuropathy, and one may regard this as added evidence for a systemic defect. The possibility that a genetic defect in lipid metabolism is responsible for hereditary nephropathy was discussed by Daneels, Kuipers and Trimbos,⁵⁷ and our Case 14 certainly had marked hyperlipidemia.

If hereditary nephropathy is caused by a systemic error of metabolism, one would expect transplanted kidneys to be affected by the same disease. We know of six such patients who underwent kidney transplantation; four survived without evidence of the disease, and in the two patients who died no evidence of hereditary nephropathy was seen at autopsy.^{58,59} The short time-interval after transplantation may, however, account for these negative findings.

One must, on the other hand, also consider that hereditary nephropathy represents a form of hereditary renal dysplasia. The subject of renal dysplasia has recently been reviewed by Bernstein;⁶⁰ it is usually associated with urinary tract obstruction. Familial cases have been reported in association with trisomy and with ocular and central nervous system malformation.⁶⁰ Bernstein offers the following hypothesis for renal dysplasia: "Dysplastic and primitive structures result from injury to the developing and immature kidney, and this injury may be determined by

heritable factors, by exogenous noxae and by associated anomalies..." Our Cases 14 and 19 had a normal karyogram and normal intravenous and retrograde pyelograms. Cartilage and primitive ducts typical of renal dysplasia were not seen in the sections of any of our five cases. However, the presence of multiple organ involvement and of fetal glomeruli suggests that hereditary nephropathy may be a form of renal dysplasia.

Only a few other studies of hereditary nephropathy by electronmicroscopy have been reported.^{22,57,61} Rome and his colleagues²² studied seven members of a family by this technique. He described severe non-uniform knobbswelling of the lamina densa, but he did not observe the granulation that we have seen. His pictures also show fusion of foot processes but to a lesser degree than in our case, and this may be explained by the fact that his cases were mainly in females. He also observed inclusion of homogeneous material in epithelial and mesangial cells and in proximal tubules, which he thought might be lipid but could be unknown substances.

Hereditary nephropathy with hematuria is probably commoner than is generally appreciated. We have under our care four other families in whom we suspect this disease, but owing to small family size and in the absence of renal biopsy the diagnosis remains unconfirmed.

We are indebted to Dr. W. J. Poznanski and Mrs. Y. Wood for amino-acid determination; to Dr. E. Liepa and Dr. S. Bencosme for advice; to Mr. Eric Bawden for photography, and to Miss Norma Rocheleau for preparing the manuscript.

Résumé

Néphropathie héréditaire avec hématurie (syndrome de Alport)

Nous avons pu démontrer la présence d'une néphropathie héréditaire chez 14 des 82 membres d'une même famille canadienne française répartis sur quatre générations. Par ailleurs, cinq autres membres de la même famille sont morts, probablement de la même pathologie. On a constaté également de la surdité chez cinq des malades souffrant de néphropathie, et chez un autre exempt de maladie rénale. Dix des 12 hommes malades sont morts d'urémie avant d'avoir atteint 40 ans. Parmi les sept femmes atteintes, une est décédée après une

grossesse. Chez deux des survivants, des examens spéciaux ne sont pas parvenus à mettre en évidence de lésions tubulaires intrinsèques, manifestées par une amino-acidurie, une acidose tubulaire, une hyperphosphaturie ou une glycosurie rénale. Ont été également exclues certaines maladies systémiques, notamment des anomalies des acides aminés sériques, une hyperoxalurie primitive, le diabète sucré et des infections. On n'a pas pu démontrer de désordres immunologiques et on a constaté que des spécimens de tissu de biopsie ne se coloraient pas par l'anti- β_2 c, l'anti-IgG et l'anti-fibrinogène marqués à la fluorescéine. Des biopsies pratiquées aux stades précoce, avancé et terminal de la néphropathie héréditaire ont mis en lumière des lésions tubulaires et interstitielles, vasculaires et glomérulaires. L'examen au microscope électronique a montré qu'il y avait épaississement prononcé des membranes basales des tubes rénaux et glomérules, une augmentation du mésangium et une fusion pédiculaire, mais n'a pas permis de montrer des "précipités immuns". On estime donc que la néphropathie héréditaire est provoquée par une erreur innée du métabolisme et qu'un métabolite non encore identifié finit par léser tant le tissu rénal que le nerf acoustique, peut-être à l'instar de certains médicaments, par ex. les antibiotiques néphrotoxiques et ototoxiques.

References

- DICKINSON, W. H.: Diseases of the kidney and urinary derangements, Part 2, Albuminuria, Longmans Green & Co. Ltd., London, 1875, p. 378.
- ALFORT, A. C.: *Brit. Med. J.*, 1: 504, 1927.
- RUSSELL, E. P. and SMITH, N. J.: *A.M.A. J. Dis. Child.*, 98: 353, 1959.
- COHEN, M. M., CASSADY, G. and HANNA, B. L.: *Amer. J. Hum. Genet.*, 13: 379, 1961.
- EASON, J., SMITH, G. L. and BUCHANAN, G.: *Lancet*, 2: 639, 1924.
- FUHRMANN, W.: *Z. Kinderheilk.*, 82: 514, 1959.
- GOLDBLOOM, R. B. *et al.*: *Pediatrics*, 20: 241, 1959.
- GOLDMAN, R. and HABERFELDE, G. C.: *New Eng. J. Med.*, 261: 734, 1959.
- GUTHRIE, L. G.: *Lancet*, 1: 1243, 1902.
- JOHNSON, W. J. and HAGAN, L. J.: *Arch. Otolaryng. (Chicago)*, 82: 166, 1965.
- KOPELMAN, H.: *Lancet*, 2: 1075, 1964.
- LOKEN, A. C. *et al.*: *Acta Paediat. Scand.*, 50: 177, 1961.
- MAMOU, M. and CATTAN, R.: *Sem. Hôp. Paris*, 28: 1062, 1952.
- METTIER, S. R.: *Arch. Ophthal. (Chicago)*, 65: 386, 1961.
- MORIN, M. *et al.*: *Sem. Hôp. Paris*, 34: 907, 1958.
- MULROW, P. J. *et al.*: *Amer. J. Med.*, 35: 737, 1963.
- OHLSSON, L.: *Acta Med. Scand.*, 174: 77, 1963.
- PERKOFF, G. T. *et al.*: *A.M.A. Arch. Intern. Med.*, 88: 191, 1951.

19. PERKOFF, G. T. *et al.*: *Ibid.*, 102: 733, 1958.
 20. REYERSBACH, G. C. and BUTLER, A. M.: *New Eng. J. Med.*, 251: 377, 1954.
 21. RINKOFF, S. S., STERN, A. and SCHUMER, H.: *J.A.M.A.*, 113: 661, 1939.
 22. ROME, L., CUPPAGE, F. E. and VERTES, V.: *Pediatrics*, 38: 808, 1966.
 23. RUSSELL, E. P. and SMITH, N. J.: *A.M.A. J. Dis-Child.*, 98: 353, 1959.
 24. SCHNEIDER, R. G.: *New York J. Med.*, 63: 2644, 1963.
 25. SHAW, R. F. and GLOVER, R. A.: *Amer. J. Hum. Genet.*, 13: 89, 1961.
 26. SOHAR, E.: *A.M.A. Arch. Intern. Med.*, 97: 627, 1956.
 27. STURTZ, G. S. and BURKE, E. C.: *New Eng. J. Med.*, 254: 1123, 1956.
 28. WHALEN, R. E. *et al.*: *Amer. J. Med.*, 31: 171, 1961.
 29. WALLACE, I. R. and JONES, J. H.: *Lancet*, 1: 941, 1960.
 30. WILLIAMSON, D. A.: *Ibid.*, 2: 1321, 1961.
 31. DUBACH, U. C., MINDER, F. C. and ANTENER, I.: *Helv. Med. Acta*, 33: 36, 1966.
 32. ROBIN, E. D., GARDNER, F. H. and LEVINE, S. A.: *Trans. Ass. Amer. Physicians*, 70: 140, 1957.
 33. LEMIEUX, G. and NEEHEM, J. A.: *Canad. Med. Ass. J.*, 97: 1193, 1967.
 34. BROWNELL, R. D. and WOLTER, J. R.: *Arch. Ophthalm. (Chicago)*, 71: 481, 1964.
 35. HAWKINS, C. F. and SMITH, O. E.: *Lancet*, 1: 803, 1950.
 36. McCLUSKEY, K. A.: *Canad. J. Surg.*, 4: 193, 1961.
 37. COLLEY, J. R. *et al.*: *Brit. Med. J.*, 1: 1266, 1958.
 38. FESSAS, P., WINTROBE, M. M. and CARTWRIGHT, G. E.: *A.M.A. Arch. Intern. Med.*, 95: 469, 1955.
 39. MICHAEL, A. F. *et al.*: *New Eng. J. Med.*, 276: 817, 1967.
 40. OUCHTERLONY, O.: *Handbook of immunodiffusion and immunoelectrophoresis*, rev. ed., Ann Arbor-Humphrey Science Publishers, 1968, p. 32.
 41. SCHAFER, I. A., SCRIVER, C. R. and EFRON, M. L.: *New Eng. J. Med.*, 267: 51, 1952.
 42. EFRON, M. L.: *Ibid.*, 272: 1243, 1965.
 43. HEPTINSTALL, R. H.: *Amer. J. Med.*, 44: 656, 1968.
 44. EDITORIAL: *New Eng. J. Med.*, 278: 1346, 1968.
 45. DIXON, F. J.: *Amer. J. Med.*, 44: 493, 1968.
 46. VERNIER, R. L. *et al.*: *In: Proceedings of the 3rd International Congress of Nephrology*, Washington, vol. 3, Clinical nephrology, edited by L. E. Becker, Albert J. Phiebig, White Plains, N.Y., 1966, p. 83.
 47. OKEN, D. E., GLASSOCK, R. J. and MERRILL, J. P.: *Immunosuppressive therapy in adults. In: Acute glomerulonephritis; proceedings of the seventeenth annual conference on the kidney*, sponsored by the National Kidney Foundation, edited by J. Metcalf, Little, Brown & Co. Inc., Boston, 1967, p. 415.
 48. KRICKSTEIN, H. I., GLOOR, F. J. and BALOGH, K.: *Arch. Path. (Chicago)*, 82: 506, 1966.
 49. SALISBURY, P. F., DUNN, M. S. and MURPHY, E. A.: *J. Clin. Invest.*, 36: 1227, 1957.
 50. PRIVE, L.: *Canad. Med. Ass. J.*, 97: 1054, 1967.
 51. KLAVINS, J. V., KINNEY, T. D. and KAUFMAN, N.: *Arch. Path. (Chicago)*, 75: 661, 1963.
 52a. BUNN, P. A., BALTCH, A. and KRAJNYAK, O.: *Ann. N.Y. Acad. Sci.*, 76: 109, 1958.
 52b. BERMAN, L. B. and KATZ, S.: *Ibid.*, 76: 149, 1958.
 53. POWELL, L. W. and HOOKER, J. W.: *J.A.M.A.*, 160: 557, 1956.
 54. HERRELL, W. E. and HEILMAN, F. R.: *Amer. J. Med.*, 2: 421, 1947.
 55. WHALEN, R. E. and McINTOSH, H. D.: *Ibid.*, 33: 282, 1962.
 56. MARIN, O. S. and TYLER, H. R.: *Neurology (Minneapolis)*, 11: 999, 1961.
 57. DANEELS, R., KUIPERS, F. C. and TRIMBOS, J. B.: *Nederl. T. Geneesk.*, 111: 1870, 1967.
 58. SMITH, E. *et al.*: *Ann. Intern. Med.*, 68: 1183, 1968 (abstract).
 59. DOSSETOR, J. B.: Personal communication.
 60. BERNSTEIN, J.: *Developmental abnormalities of the renal parenchyma—renal hypoplasia and dysplasia. In: Pathology annual*, vol. 3, edited by S. C. Sommers, Appleton-Century-Crofts Inc., New York, 1968, p. 213.
 61. ANTONVYCH, T. T. and AIKAWA, H.: *Lab. Invest.*, 12: 857, 1963 (abstract).
 62. GOYER, R. A. *et al.*: *Amer. J. Med. Sci.*, 256: 166, 1968.

ERRATA

In the article: "Rheumatoid Arthritis: Comparison of Treatment with Monophenylbutazone and Phenylbutazone" by Woodbury, Turner and Tiongson (*Canad. Med. Ass. J.*, 101: 801, 1969) in Table II, Group A, column 3 should be MBZ and column 5 should be PBZ; in Group B, column 3 is PBZ and column 5 is MBZ.

Table IV should be as follows:

Symptom	ASA	PBZ	MBZ
Nausea	7	1	1
Dyspepsia	6	2	1
Vomiting	4	—	1
Rash	1	1	—
Pruritus	1	—	—
Headache	2	2	1
Tinnitus	1	—	—
Lightheadedness	3	—	—
Vertigo	—	—	1
Increased thirst	1	—	—
Ankle edema	—	1	—
Weight gain	—	1	—
Depression	—	1	—

Table IV in the text should be designated Table V and should be cited in Col. 1, p. 803, seven lines from the bottom "... patient's condition (Table V)." The last sentence (p. 803, column 3) should read: "It would be interesting to try the effects of monobutazone in patients with more severe illness."

ANNOUNCEMENT OF EXAMINATIONS

Examinations are held each autumn by The Royal College of Physicians and Surgeons of Canada. Fellowship examinations are conducted in Internal Medicine and in General Surgery with modifications of these Fellowship examinations for certain specialties. Certification examinations are conducted in the approved medical and surgical specialties. **Applications for the 1970 examinations must be submitted before March 31, 1970.**

Prospective candidates who would like to obtain a preliminary assessment of their past and proposed training in preparation for the examinations of this College may apply for such an assessment at any time of the year.

The following material may be obtained from the College headquarters:

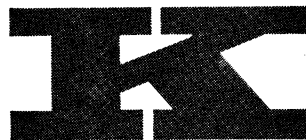
- Regulations and Requirements of Graduate Training relating to the Examinations. Applicants should indicate whether they desire copies of the Medical or Surgical regulations.
- List of Canadian hospitals approved by the College for postgraduate training.
- Application forms for preliminary assessment of past and proposed training.
- Application forms for the examinations
- Fellowship and Certification.

Address all communications to:

The Secretary

The Royal College of Physicians
and Surgeons of Canada

74 Stanley Avenue, Ottawa 2, Canada



KALFORTE*

An inexpensive pleasant tasting prevention for potassium deficiency.

- Easy to digest
- Cherry flavored
- Contains no sugar
- Effectively prevents hypokalemia during administration of chlorothiazide, mineralocorticoids and digitalis
- One tablespoon daily is approximately equal to the potassium found in either of 2 bananas, 3 glasses of orange juice, 30 cups of tea or 2 cups of whole milk.

*Contains elemental potassium (as potassium acetate, potassium bicarbonate, potassium citrate, potassium gluconate).

Available in 16 ounce bottles.

Literature and samples on request

TEXCAN PHARMACEUTICALS LTD.

50 Raleigh Ave. Scarborough, Ontario