FAMILIAL NEPHROPATHY WITH SPLENOMEGALY

S. J. FLEISHMAN, M.B., M.R.C.P. (EDIN.); N. W. LEVIN, M.B., B.CH. (RAND); G. S. GETZ, B.SC. (HON.), M.B., B.CH. (RAND); and B. M. WEINBREN, B.SC. (HON.) (LOND.), M.A., B.M., B.CH. (OXON.)

Departments of Medicine and Chemical Pathology, University of the Witwatersrand, Johannesburg

The existence of hereditary nephropathy was recognized in the 19th century, and in 1930 Mitchell[1] was able to review no less than 33 papers dealing with this subject since 1874. More recently, a number of reports have appeared describing genetically determined renal disease, with manifestations ranging from symptomless proteinuria and microscopic haematuria to uraemia, hypertension, or the nephrotic syndrome. A remarkable feature of many of these has been the coexistence of other defects, especially nerve deafness and abnormalities of the eye, such as spherophakia and cataract. In general, males appear to have been more frequently and more severely affected than females. It should be stated that certain forms of renal tubular disease, such as the Fanconi syndrome and renal tubular acidosis, which may also be genetically determined, are not under consideration here.

Perkoff *et al.*[2] were able to trace 134 of 232 direct descendants of a single person, and found that no less than 50 of them suffered from proteinuria, pyuria and hypertension. In this family there were 7 cases of fatal uraemia (all in males), 8 of progressive nerve deafness, and 19 of mitral-valve disease. Autopsies performed on 2 patients revealed pyelonephritis. Reyersbach and Butler[3] reported 8 patients with congenital haematuria, 3 of whom had nerve deafness, in 4 unrelated families. Renal biopsy in 1 patient showed no abnormality other than red cells in the tubules. Many cases of nerve deafness, eye defects, and nephritis were present in the relatives of one of these groups.

Sohar[4] described an Israeli family in which 4 brothers and a sister had proteinuria with erythrocytes, leucocytes and granular casts in the urine. All the brothers had elevated blood-urea levels, decreased urine-concentrating power and urea clearances, and nerve deafness. In addition, 2 had slight hypertension, 2 spherophakia and 2 congenital posterior cataracts. The mother and 2 maternal uncles also suffered from nerve deafness and kidney disease. Goldbloom *et al.*[5] reported a mother and 3 sons of Jewish stock who had renal disease. Two of the sons had nerve deafness and one of these had bilateral anterior sub-capsular cataract. Postmortem examinations on the 2 sons who died showed severe pyelonephritis.

Vernier *et al.*[6] presented the results of a study of a family in which all 4 children suffered from either 'pure' nephrosis or chronic glomerulonephritis with the nephrotic syndrome. The presence of nephropathy was anticipated in the fourth of these children, and the first urine voided after birth was shown to contain protein and a few red

and white cells. Biopsies of the kidneys were done in all 4 patients and these revealed changes ranging from the normal to advanced glomerulonephritis. Wallace and Jones[7] described a family in which 3 children died of chronic renal disease and hypertension; autopsies were carried out on 2 of the children, and chronic glomerulonephritis was found. There was increased amino-aciduria in 1 of these as well as in 2 surviving siblings and in both parents.

It is our purpose to present the details of a Jewish family consisting of a father and 3 sons who suffered from apparently benign proteinuria. A renal biopsy was carried out in one of the sons; this showed histological abnormalities of the glomeruli.

CASE REPORT

L.W., the father, aged 57, had been found to have proteinuria at a routine insurance examination 8 years previously. Five years later a papilloma of his bladder was fulgurated and this operation was complicated by an air embolus resulting in partial hemiplegia. S.W., P.W., and H.W., his sons aged 27, 24, and 21 respectively, were also found, on routine examination, to have proteinuria. This discovery led to a more detailed study.

Abnormalities of the urine were not present in 2 of the father's sisters nor in his brother. Findings in a third sister were unobtainable. His wife's urine was normal. Neither L.W. nor his 3 sons had suffered from renal or other disease except for exanthemata of childhood including scarlet fever. Apart from slight enlargement of the spleen in S.W. and H.W., the physical examinations were normal and the blood pressures were not raised. The proteinuria, which was present in recumbency in each instance, increased on standing. The amount of protein excreted in 2 24-hour periods is shown in Table I. Glycosuria was not present and bacterial cultures of

TABLE I. URINARY PROTEINS

	L.W.	*S.W.*	*P.W.*	*H.W.*
Protein excretion* (mg. per 24 hours)	348	388	356	823
	432	204	263	—
Mucoproteins	Faint	Faint	Faint	Faint
	trace	trace	trace	trace

* In all 4 cases albumin accounted for 70 - 80 per cent of the urinary protein excretion.

the urine were negative. Microscopic examination of the urine showed increased numbers of red cells, white cells, and casts. The casts were mainly hyaline and granular, but occasional doubly refractile casts were also seen. Addis counts

TABLE II. ADDIS COUNTS (TWO 24-HOUR SPECIMENS)

		L.W.	*S.W.*	*P.W.*	*H.W.*
Leucocytes (millions)	1st	1·74	3·90	4·40	3·81
	2nd	0·92	0·92	9·40	—
Erythrocytes (millions)	1st	41·60	69·60	724·68	55·40
	2nd	25·34	1·73	2,001·62	—
Casts (thousands)	1st	1,740	173	2,820	952
	2nd	9,620	188	5,040	—

confirmed the considerable increase in formed elements, especially red cells (Table II). Amino-acid chromatography of the urine showed that amino acids were present in normal amounts and no abnormal amino acids were found.

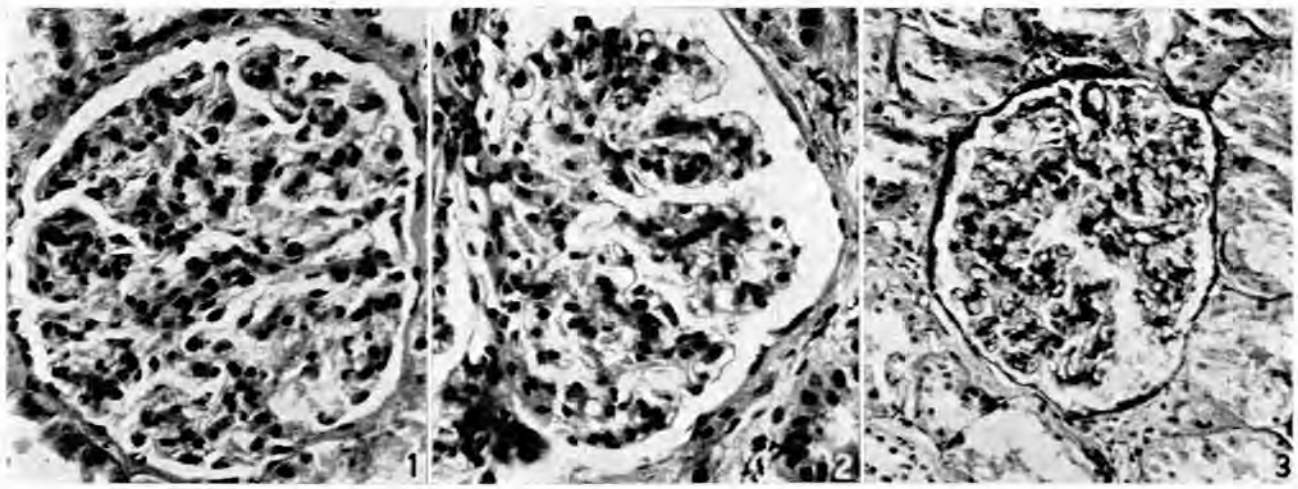
Standard concentration and dilution tests of the urine were carried out on L.W., S.W., and P.W., but not on H.W., who had gone abroad by the time this study was undertaken. The urine could be concentrated to 1019, 1021 and 1023 and diluted to 1002, 1003 and 1001 respectively. The corresponding urea-clearance values were 86%, 103% and 95% of normal. Results of the phenolsulphothalein-excretion tests were normal.

The following investigations were also normal in all 4 patients: haemoglobin, packed-cell volume, white-cell and differential counts, erythrocyte sedimentation rate, prothrombin index, serum urea, potassium, sodium, chloride, bicarbonate, cholesterol, calcium, inorganic phosphorus, alkaline phosphatase and uric acid. The serum-protein electrophoretic patterns were normal and screening tests for syphilis were negative. The urinary electrophoretic pattern showed 70 - 80% of albumin in each case (Table I). Malrotation of the kidneys was demonstrated on intravenous urography in L.W. and P.W., but this examination was otherwise normal in all 4 patients.

Percutaneous renal biopsy was performed on H.W., chosen because his proteinuria was most marked. The glomeruli proved to be larger and more cellular than normal, and contained excessive numbers of polymorphonuclear leucocytes as well as a few macrophages (Fig. 1). There was separation of the loops into quite distinct tufts (Fig. 2) with adhesion of some of these to the capsule. Several small areas of hyalinization were also present in the glomeruli. Periodic-acid Schiff preparations revealed thickening of the basal membrane (Fig. 3). The tubules were normal. These findings were regarded as compatible with glomerulitis, such as is seen in the recovery stage of acute glomerulonephritis.

DISCUSSION

A distinction must be drawn between those familial nephropathies which are the result of a common environmental factor, such as streptococcal infection or a toxin, and those which are inherited. This may not be easy when all the patients occupy the same house and their relatives



Figs. 1 - 3. See text.

are unaffected. Although first discovered in adult life, there is no reason to believe that the renal disease in L.W. and his 3 sons was caused by external agents and it is considered more likely to be of hereditary origin.

Because of the lack of significant impairment of renal function in the father at the age of 57, the disease may be expected to follow an equally benign course in the sons. A further reason for expecting this is the relatively mild degree of pathological change demonstrable at renal biopsy in the son with the most marked proteinuria. On the other hand, the possibility that renal insufficiency will ensue in the course of time cannot be completely excluded.

The splenomegaly present in S.W. and H.W. is a feature which has not previously been noted in association with hereditary nephropathy, but nevertheless it does not seem likely that it is merely coincidental. The true significance of this unusual finding remains a matter for speculation.

It is interesting to note that renal disease, especially pyelonephritis, has recently been described in combination with Marfan's syndrome[8] which may also, in some cases at least, be a genetically determined condition.[9] However, evidence of Marfan's syndrome was not present in our patients, nor was it mentioned in any of the other reports. Another aspect which could be relevant from the genetic view-point is the relatively high proportion of Jewish families among those suffering from hereditary renal disease, viz. the families reported by Sohar[4] and Goldbloom *et al.*,[5] and the one we describe. Whether this represents a real racial susceptibility is uncertain.

On reviewing the histological appearances of the kidneys in those examples of hereditary nephropathy referred to, it is possible to classify them into cases of pyelonephritis and into those which seem to conform to the diagnosis of glomerulonephritis in its various phases. If this interpretation is correct, all these cases of hereditary renal disease fall into two categories despite their widely differing clinical presentations.

It is even possible that the relationship between these two is closer than is apparent, in view of the occurrence of eighth-nerve and eye disorders in both. This 'unitarian concept', as far as the various forms of glomerulonephritis are concerned, is supported by Vernier *et al.*[6] In the family he studied, the clinical manifestations included transient 'pure' nephrosis, persistent 'pure' nephrosis, so-called mixed nephrosis-nephritis, and chronic glomerulonephritis. At biopsy, the corresponding histological features ranged from the normal to severe chronic glomerulonephritis.

SUMMARY

A family is described in which the father and his 3 sons were found to have symptomless proteinuria.

Unexplained splenomegaly was present in 2 of the sons.

Addis counts revealed an increase in formed elements, especially red cells, in all 4 patients.

A renal biopsy was performed in the most markedly affected of the 4; this showed a mild glomerular lesion suggestive of glomerulonephritis.

In all probability the nephropathy in this family is hereditary in origin.

Thanks are due to Dr. John Barlow who performed the renal biopsy, to Dr. Priscilla Kincaid-Smith and Dr. John Gluckman who examined the histological preparations, and to Miss O. A. Abrahams for the quantitative determination of the amino acids. We are grateful to Prof. H. B. Stein who afforded us facilities for many of the laboratory investigations and to Prof. G. A. Elliott for his interest. Mr. M. Ulrich prepared the photographs.

REFERENCES

1. Mitchell, A. G. (1930): A.M.A. Amer. J. Dis. Child., **40**, 145.
2. Perkoff, G. T., Stephens, F. E., Dolowitz, D. A. and Tyler, F. H. (1951): A.M.A. Arch. Intern. Med., **88**, 191.
3. Reyersbach, G. C. and Butler, A. M. (1954): New Engl. J. Med., **251**, 377.
4. Sohar, E. (1956): A.M.A. Arch. Intern. Med., **97**, 627.
5. Goldbloom, R. B., Fraser, F. C., Waugh, D., Aronovith, M. and Wiglesworth, F. (1957): Pediatrics, **20**, 241.
6. Vernier, R. L., Brunson, J. and Good, R. A. (1957): A.M.A. Amer. J. Dis. Child., **93**, 469.
7. Wallace, I. R. and Jones, J. H. (1960): Lancet, **1**, 941.
8. Loughridge, L. W. (1959): Quart. J. Med., **28**, 531.
9. Sinclair, R., Kitchin, A. and Turner, R. (1960): *Ibid.*, **29**, 42.