Current Practice

Recurrent Haematuria in 17 Children

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Haematuria is a common presenting symptom in paediatric practice. Alarming to both parents and doctors, it is even more so when recurrent. Children with the recurrent complaint tend to be subjected to extensive urological investigations, prolonged restrictions of activity, and special diets. Harrison and his colleagues (1966) regarded glomerulonephritis as the commonest cause of non-traumatic haematuria in children of all age groups and most prevalent between 5 and 10 years. This study investigates the clinical, morphological, and functional features in a group of children with recurrent haematuria.

Material and Methods

A total of 58 children with haematuria not due to clinical acute glomerulitis were admitted to the medical wards of the Royal Hospital for Sick Children, Glasgow, in the six-year period 1962–7. The great majority of these ceased to have further episodes and were not included in this study. Eleven boys and six girls with recurrent haematuria underwent renal biopsy. The age at onset of their haematuria varied from 3 to 10 years. Each child was followed up to July 1968, the longest period being seven years and the shortest one year. The mean follow-up period is four years.

Percutaneous renal biopsy was carried out at least once on each child under general anaesthesia with the use of a modified Vim–Silverman needle. The core of renal tissue obtained was fixed in formal saline, embedded in paraffin, cut in thin sections, and stained by haematoxylin and eosin, periodic-acid Schiff (P.A.S.), and Marshall Scarlet Blue stains.

The serum β-I-C globulin level was estimated in 11 children with Hyland Immunoplates. Eight of these children had gross haematuria and three had microscopic haematuria at the time. The creatinine clearance was estimated in 14 children at the end of the follow-up period. Urine specimens from the other members of the immediate family of each patient were tested with Labstix.

If the Labstix showed doubtful or positive results the urine was further examined by the salicylsulphonic acid test for protein, and a microscopical investigation was made for cells and casts.

Results

Clinical

A history of recent upper respiratory infection was obtained from nine of the children with haematuria. In only two children (Cases 5 and 11) was there evidence of streptococcal infection as judged by throat swabs and antistreptolyin O (A.S.O.) titres. Exacerbation of haematuria was observed in three children in the evening and after exercise in one further child. All children were free from oedema. Systemic blood pressure and blood urea levels were normal in every case. A complaint of loin pain was made by four children (three female and one male), of backache by two further children, and of generalized abdominal pain by four children (Table I).

Intravenous urography was normal in 16 children, but in one child (Case 5) duplex kidneys were shown. Culture of a

TABLE I.—*Clinical Data*

Case No.	Sex	Age at Onset (years)	Years of Follow-up	No. of Episodes	Relation to U.R.I.	Exacerbation of Haematuria	Duration of Gross Haematuria	Abdominal Pain
1	M	3	4	Many	+	In the evening	3–4 days	No
2	M	10	5	10+	–	–	2 days	(L) loin
3	M	3	7	3+	+	–	Few weeks	No
4	M	5	6	10+	–	–	2–3 weeks	Generalized
5*	F	7	2	20+	–	–	1 day	(R) loin
6*	F	6	5+	Many	–	+	<1 day	Both loins
7	M	9	1+	Many	–	+	<1 day	No
8*	F	7	7	Many	+	–	4–5 days	Generalized
9*	F	3	5	Many	–	–	Few days	No
10	F	10	1+	5+	+	–	1 week	(R) loin
11	M	9	5+	Many	+	–	1 week	No
12	M	7	7+	7+	+	–	1 week	Generalized
13	M	7	1+	8+	–	–	2–4 days	Backache
14*	F	8	1+	Many	–	+	1 day	Backache
15	M	7	2+	10+	+	–	1 week	Generalized
16*	M	10	1	Many	+	After exercise	2–3 days	No
17	M	6	1	Many	+	+	1–2 days	No

* No microscopic or chemical haematuria between attacks (see Table II).

TABLE II.—*Laboratory Data*

Case No.	Cast in Urine	Urinary Abnormality between Attacks: Albumin	Urinary Abnormality between Attacks: R.B.C.	Highest Blood Urea (mg./100 ml.)	Highest A.S.O. Titre Todd Units/ml.	Beta-I-C Globulin (mg./100 ml.)	Mantoux	I.V.P.	Cystoscopy
1	+	+	+	20	50	–	–	Normal	Normal
2	+	+	+	40	50	–	–	Normal	Normal
3	+	Trace	+	20	50	150	+ B.C.G.	Normal	Not done
4	+	±	±	30	125	165	–	Normal	Not done
5	–	–	–	33	1,250	–	–	Duplex kidneys	Normal
6	+	–	–	23	50	180	–	Normal	Normal
7	+	Trace	+	37	200	240	–	Normal	Normal
8	+	Trace	–	40	50	110	–	Normal	Normal
9	+	–	–	33	50	–	+ B.C.G.	Normal	Normal
10	+	±	±	33	125	–	–	Normal	Not done
11	+	Trace	+	40	500		–	Normal	Not done
12	+	Trace	Occ.	33	200	150	+ B.C.G.	Normal	Not done
13	+	±	±	43	125	240	–	Normal	Not done
14	–	–	–	25	125	140	–	Normal	Normal
15	+	Trace	+	35	125	170	–	Normal	Not done
16	–	–	–	28	125	170	–	Normal	Normal
17	–	±	±	38	125	170	–	Normal	Normal

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midstream urine specimen was negative in all 17 children. Granular casts and/or red cell casts were found in 13 of the 17 children, all of whom had been initially investigated in other hospitals. Microscopic haematuria and traces of proteinuria were present between gross episodes either on some occasions or persistently in 12 of the 17 children. No abnormality was detected when cystoscopy was carried out on 10 children (Table II), including the four without a record of casts in the urine. Audiograms were carried out in seven children, and no perceptive deafness was detected.

Histology

The mean glomerular count of the 22 renal biopsy specimens from all 17 children was 20, and only two yielded less than 10 glomeruli (eight each). The histology of the renal tissue appeared virtually normal in five children on light microscopy. A mild degree of proliferative glomerulonephritis, exhibiting slight increase in endothelial cells, was present in eight children: in one of these the lesion was focal (Fig. 1). In five biopsies (two of which were repeat biopsies on children who previously had shown evidence of a mild proliferative glomerulonephritis) there was some increase of P.A.S.-positive material, particularly in axial regions, in association with some axial cell proliferation (Fig. 2). This was regarded as evidence of a previous or long-continued proliferative lesion. In the five children in whom serial renal biopsies were performed over a period of up to five years this was the only progressive change noted, and it was not severe. In one case a well-established proliferative glomerulonephritis of moderate degree was seen, and in this specimen one epithelial crescent was observed (Fig. 3). One arteriole with apparent thickening of the wall was noted in another specimen, but the muscle coat rather than the endothelium was affected. This could have been an artefact due to tangential cutting, and in point of fact in this case definite glomerular lesions were demonstrable.

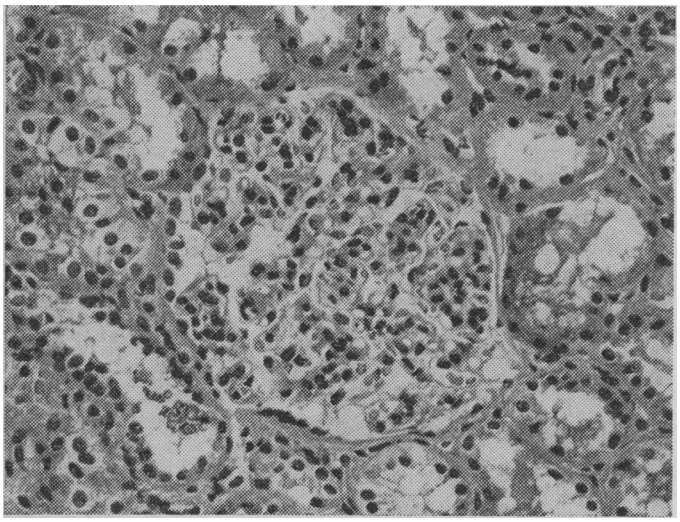

FIG. 1.—This glomerulus exhibits slight proliferation of endothelial cells with no obvious progressive changes. A few polymorphs are present in the glomerular capillary and a group of red blood cells is demonstrated within a tubule just external to the glomerulus. (Haematoxylin and eosin. ×270.)

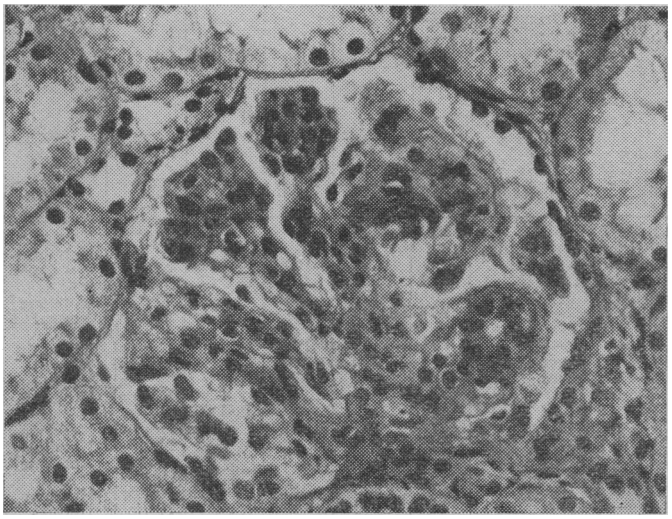

FIG. 2.—Proliferation of endothelial or mesangial cells is seen in this figure, and in the mesangial regions increased amounts of P.A.S.-positive material are present. (Periodic-acid-Schiff. ×450.)

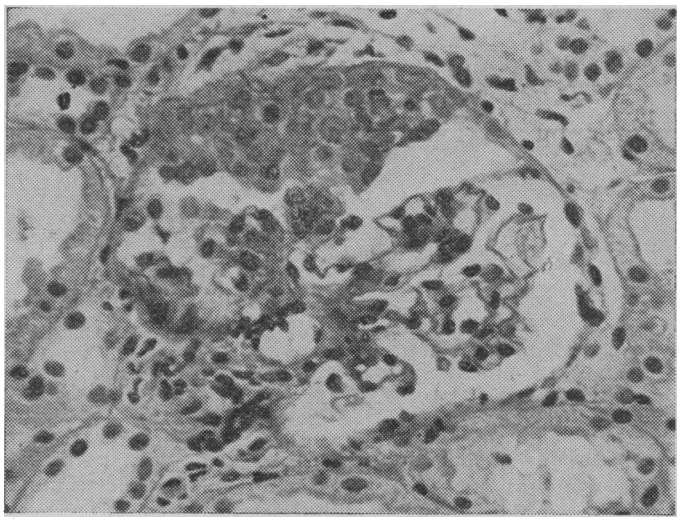

FIG. 3.—This glomerulus shows only minor endothelial cell proliferation but a small epithelial crescent is also demonstrated. (Haematoxylin and eosin. ×250.)

Biopsies were not usually performed at the height of haematuria, and some biopsies were performed in the absence of haematuria. This might possibly explain the normal appearance of the glomeruli in at least two cases. Casts were found in the urine from three of the five children with normal renal histology.

Present Clinical Status

Table III shows the present condition of these children. The two children found to have proteinuria in excess of 0·5 g./24 hours (Cases 3 and 11) have each followed a relapsing course for five years or more. These two children had definite but mild glomerulonephritis on renal biopsy. Most children whose proteinuria was less than 0·2 g./24 hours followed a milder clinical course and with the exception of Case 15 showed only slight histological changes. The serum creatinine level was

TABLE III.—*Present Status*

Case No.	Recurrence of Macroscopic Haematuria	Persisting Microscopic Haematuria	Persisting Proteinuria (mg./day)	Serum Creatinine (mg./100 ml.)	Creatinine Clearance (ml./min./1·73 sq.m.)
1	+	+	+	0·67	Not done
2	Not for 1 year	–	–	0·80	Not done
3	+	+ + +	700–3,000	0·55	88
4	+	–	–	0·65	103
5	Not for 1 year	–	–	0·65	93
6	Not for 1 year	–	50	0·65	99
7	Not for 1 year	–	–	0·70	101
8	Not for 2 years	–	50	0·67	91
9	Not for 5 years	–	–	0·70	Not done
10	+	+	360	0·61	112
11	+	+ +	700	0·67	129
12	Not for 2 years	+	270	0·52	120
13	+	+	–	0·61	93
14	+	–	140	0·67	90
15	+	+	130	0·70	86
16	+	–		0·75	95
17	+	+	–	0·40	103

normal in all children and creatinine clearance (corrected to 1·73 sq. m.) was within normal limits in each of the 14 children on whom this test was carried out. Seven children had been free of recurrent macroscopic haematuria for one or more years at the end of follow-up. Three of these continued to have persistent proteinuria with or without microscopic haematuria. Prolonged bed rest and antibiotics did not seem to influence the haematuria.

No family history of haematuria or renal disease was elicited in any of the 17 children. A total of *seventy* members of the immediate families were screened and tested with Labstix. The only positive results were in the mother and two half-sisters of one child, who were found to have microscopic haematuria.

Discussion

Baehr (1926) described a benign form of haemorrhagic nephritis without oedema and hypertension, which had a good prognosis despite prolonged or recurrent haematuria. Wyllie (1955) and Livaditis and Ericsson (1962) emphasized the benign nature of haematuria in childhood, but had no knowledge of the histological findings in the kidney. Ayoub and Vernier (1965), having carried out renal biopsies on 14 of 17 similar children who had been followed up for 2 to 10 years, concluded that this was a benign condition. The majority of renal biopsies in the present series revealed only slight proliferative changes in the glomeruli. Only one child had a glomerulonephritis of moderate severity, but even here no evidence of significant glomerular obliteration was seen. In five children in whom serial renal biopsies were carried out two showed mild and possibly functionally insignificant progressive changes while the other three revealed no progressive change.

Fourteen children were found to have a normal creatinine clearance at the end of the follow-up period (mean four years), and all children had normal serum creatinine and urea levels and systemic blood pressure and were of average height at that time. Seven children ceased to have haematuria for periods varying from one to five years. These findings would suggest that recurrent haematuria as presented here does not usually indicate rapidly progressive nephritis in children. It is not possible to exclude the possibility that some of these children had a slowly progressive condition, and only ultra long-term follow-up can supply more information. In our experience haematuria may recur after an interval of two years, and proteinuria with or without microscopic haematuria may persist after cessation of macroscopic haematuria. However, a boy aged 10 years with recurrent haematuria who subsequently developed the nephrotic syndrome was recently referred to our care. He was found to have low serum β-I-C globulin and mixed membranous and proliferative lesions on renal biopsy. It is obviously wrong to be too dogmatic about the "benign" nature of this condition. This opinion is shared by Singer *et al.* (1968).

Preceding upper respiratory tract infection was present in nine of the 17 children with recurrent haematuria. The lack of evidence of streptococcal infection in the great majority and the normal serum β-I-C globulin levels might suggest that the glomerulonephritis may have been of viral aetiology. Bates *et al.* (1957) reported 10 cases of acute nephritis not associated with group A haemolytic streptococcal infection, and Tina *et al.* (1968) reported five cases with normal serum β-I-C globulin. Some of these cases had no evidence of streptococcal infection. Bodian *et al.* (1965) found no distinct abnormality in renal biopsy specimens from children with recurrent haematuria associated with acute glomerulonephritis or anaphylactoid purpura or of unknown cause. In an electron microscopical study of renal biopsy specimens from children with recurrent haematuria Singer *et al.* (1968) found electron-dense deposits in the basement membrane of glomerular capillaries similar to those of resolving acute glomerulonephritis.

Recurrent haematuria probably does not constitute a distinct type of glomerulonephritis. In our experience patients with post-streptococcal acute glomerulonephritis and depressed serum levels of β-I-C globulin in the acute stage and a normal level after convalescence may have normal serum β-I-C globulin when recurrent haematuria not associated with streptococcal infection occurs months later.

A high familial incidence of recurrent haematuria was noted by McConville and her colleagues (1966). These workers entrusted the testing for haematuria to parents and siblings, whose urines were screened with Hemastix over a period of seven days. The fresh urines from first-degree relatives of our patients were tested and the results indicated a much lower familial incidence (only the mother and two half-sisters of one child). Since these urines were not screened over a period of consecutive days this procedure might have overlooked a condition of intermittent haematuria.

Little and her colleagues (1967) described three young women with haematuria and loin pain found to have arteriolar lesions on renal arteriography and renal biopsy. Possible arteriolar changes were noted in one of our cases, but glomerular lesions were seen in the same case. It is thought that the arteriolar changes in this case were due to an artefact rather than of aetiological significance.

Ferris *et al.* (1967) suggested that in recurrent haematuria if casts were found in the urines a renal biopsy would be more helpful than repeated cystoscopies. Our experience would substantiate their views. It is obvious that the understanding of this common condition in childhood is still far from adequate, and much more work has to be done in order to separate this heterogeneous group of disorders and to know the long-term prognosis of each condition.

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