Recurrent Haematuria in Childhood

A Five-year Follow-up

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In 1965 Bodian *et al.* reported observations on 46 children with recurrent haematuria investigated by renal biopsy. The cases were classified according to the type of onset of haematuria into one of three groups: (1) no definite illness (36 cases); (2) attack of anaphylactoid purpura (7 cases); and (3) acute glomerulonephritis (3 cases). The biopsy specimens were examined by orthodox histological, immunohistological, and histochemical techniques. Focal segmental glomerulonephritis was the most common lesion in the first and third groups, but the second group usually had more generalized lesions.

This report presents 5-year follow-up observations on these children, undertaken in the hope that it would provide some insight into the natural history of recurrent haematuria and focal nephritis. Patients with an obvious cause for the haematuria had been excluded from the original study. Included in this report are patients who had continuing haematuria as well as those who subsequently became asymptomatic. Attention was focused on the 36 patients in Group 1 (no specific illness preceding the first episode of haematuria), Groups 2 and 3 being included for comparative purposes.

Material and Methods

Of the 46 patients in the original study, 36 returned for review: some details of their original illness are given in the Table. Reassessment of their renal status included an interim history; general physical examination; complete blood count; determination of sedimentation rate, ASO titre, serum β_{1C} -globulin, and blood urea nitrogen; urinalysis; urine culture; 24-hour urine for protein; urine amino acid chromatography; measurement of clearance of creatinine, and appropriate x-ray investigation. Renal biopsy was repeated in 6 cases. In an effort to uncover other unknown affected family members, the urine of all other family members was checked with 'Hemastix'.

Results

All 12 girls and all but one of the 24 boys (ranging in age from 6 to 20 years) were in good health. Case numbers are the same as those used in the original report (Bodian *et al.*, 1965).

Group 1. 28 of the 36 patients (78%) in Group 1 were reassessed. In 1 of the 8 girls (Case 29) and 13 of the 20 boys (Cases 2, 5, 6, 14, 15, 19, 20, 24, 25, 27, 28, 30, 36) macroscopical haematuria has persisted, though in the girl this has diminished and for the past 2 years only microscopical haematuria has been found. One of the boys has had symptoms for 20 years (Case 2), and the other 12 for more than 5 years. Thus, after 5 years, half of the patients traced do not have haematuria microscopically, macroscopically, or by 'Hemastix' examination.

No haematuria. 14 children (Cases 1, 9, 10, 12, 13, 16, 17, 21, 22, 23, 26, 31, 32, 33) were asymptomatic. The haematuria had lasted from less than 1 year to 6 years. Exercise and infection of the upper respiratory tract had been the main association preceding bleeding. Now, activity of this group is unrestricted, and all have their share of infections of the upper respiratory tract. Generally, the haematuria gradually disappeared, slowly becoming less frequent. 3 boys had a family history of nephritis or other renal disease (Cases 10, 17, 21). 6 of the 14 patients now free of haematuria initially had persistent microscopical haematuria between the bouts of gross haematuria.

Creatinine clearance, corrected to 1.73 m^2 , ranged from 98 to 188 ml./min., with an average of 121 ml./min. Of these 14 children, 8 had been taking antibiotics prophylactically, either continuously or with infections of the upper respiratory tract for a period in the past, but were not taking these drugs at the time of evaluation. One patient had been given a short course of steroid therapy.

TABLE
Details of Initial Illness in 36 Cases of Recurrent Haematuria

Group	Total in Group	Males	Family History of Renal Disease	Onset Before Age 4	Persistent Microscopical Haematuria Initially
<i>Group 1: No specific illness preceding haematuria</i>					
With haematuria	14	13	7	8	11
Without haematuria	14	7	2	2	6
<i>Groups 2 and 3: Glomerulonephritis or anaphylactoid purpura</i>					
With haematuria	6	3	0	0	6
Without haematuria	2	1	1	0	2

Cases 21, 22, and 31 had subsequent renal biopsies. In Case 21 focal glomerulonephritis was again reported. The renal biopsy performed in 1963 on Case 22 was reinterpreted as showing generalized diffuse glomerulonephritis, having originally been thought to show a focal and segmental glomerulonephritis. In Case 31 the biopsy specimen obtained in 1963 showed less extensive changes than the initial biopsy specimen.

Continuing haematuria. Of the 14 patients with continuing haematuria, none had gross physical abnormalities. The duration of haematuria ranged from 5 to 20 years. 10 of the 14 patients had had haematuria for 7 or more years. All patients are taking antibiotics prophylactically. 7 of the 14 patients (Cases 2, 14, 15, 19, 24, 25, 27) have a family history of nephritis or other renal disease, 3 of whom have a family history of deafness. Cases 2 and 15 now have obvious nerve deafness. Of the 7 patients with a family history of haematuria, 5 have several clinical features in common: all are boys whose haematuria appeared early in life and was associated with episodes of infection of the upper respiratory tract but not with exercise; microscopic haematuria was present between bouts of gross haematuria, usually associated with proteinuria and cylindruria.

Case 27, whose brother has microscopic haematuria has a platelet disaggregation defect (Hardisty and Hutton, 1967). Both boys and their father have had frequent nose bleeds.

Eleven of the 14 children with continuing haematuria had had persistent microscopic haematuria between bouts of gross haematuria at the time of the original report. Proteinuria is present only in children with continuing disease, but despite this, the creatinine clearances have remained within normal limits, ranging from 98 to 229 ml./min. per 1.73 m^2 , with an average of 138 ml./min.

Only 3 patients had renal biopsy on follow-up evaluation (Cases 5, 19, 20). The findings were essentially the same as the previous reports.

Groups 2 and 3. All but 2 (Cases 43 and 46) of the 10 patients in these two groups were reassessed (80%). Their ages now range from 12 to 19 years. The age at onset ranged from 2 to 11 years. All of these patients had persistent microscopic haematuria when initially evaluated. Both patients with an original diagnosis of glomerulonephritis have continuing intermittent macroscopic haematuria, and 4 of the 6 with an original diagnosis of anaphylactoid purpura have haematuria. 3 of these patients are taking antibiotics prophylactically and 1 is receiving steroids. Only 2 patients reported onset of gross haematuria with infection of the upper respiratory tract. 1 patient (Case 42) recently died after prolonged renal failure.

None of the 8 patients had a family history of haematuria except 1 (Case 40), whose brother had had haematuria on one occasion, also associated with anaphylactoid purpura. The only patient with a significant abnormality among all these reassessed by urine amino acid chromatography was a girl who had anaphylactoid purpura but has been asymptomatic for several years. She had transient glycinuria. Creatinine clearances range from 101 to 204 ml./min. per 1.73 m^2 , with an average of 127 ml./min. (excluding Case 42 whose last creatinine clearance was 17 ml./min.). One patient (Case 37) had a second biopsy which showed slow progression of glomerulonephritis.

Observations. The groups could not be classified on the basis of laboratory tests. Complete blood count, sedimentation rate, ASO titres, serum β_{1C} -globulin determinations, and urine amino acid chromatography yielded results within normal limits in all patients. There was no

difference in blood urea nitrogen or creatinine clearances among the groups. Creatinine clearances ranged from 98 to 229 ml./min. per 1.73 m^2 , with an average of 138 ml./min. in the group that has continuing haematuria, and 98 to 188 ml./min. per 1.73 m^2 , with an average of 121 ml./min. in the asymptomatic group, and 101 to 204 ml./min. with an average of 127 ml./min. in the glomerulonephritis and anaphylactoid purpura group.

Twenty-four hour urine protein excretion varied; it was as high as 14.5 g. in Case 2; otherwise, the range was from an insignificant level to 2.4 g./24 hours. All patients with moderate to severe proteinuria had persistent haematuria or were in Groups 2 or 3. No patient in the group with no haematuria had more than 60 mg. protein in the 24-hour urine specimen.

All members of the patients' immediate families were given 'Hemastix' for testing at home for 1 week. The examinations revealed no unknown family members with haematuria.

Discussion

The cause of focal nephritis is unknown. Presumably, the disease is the end result of many different renal insults. Many pathological states may be associated with focal glomerular lesions on biopsy. Non-streptococcal glomerulonephritis and presumed viral disease can cause a similar clinical picture (Bates, Jennings, and Earle, 1957). Focal changes similar to those originally described have been seen in patients convalescing from streptococcal glomerulonephritis (Bodian *et al.*, 1965). Recurrent haematuria and focal nephritis certainly have been seen in patients with familial nephritis. The earliest renal lesion seen in patients with familial nephritis and deafness (Alport's syndrome) is a focal glomerular lesion (White, Parsons, and Walt, 1964). Familial nephritis may be manifested initially by bouts of gross haematuria triggered by infection of the upper respiratory tract or streptococcal infections. The picture may even mimic post-streptococcal glomerulonephritis. A normal serum β_{1C} -globulin level would be a factor against the diagnosis of post-streptococcal glomerulonephritis, since the serum level decreases strikingly in this disease but remains normal despite gross haematuria in children with familial nephritis (Wasserman *et al.*, 1965). Other pathological states that may also be associated with focal glomerular lesions shown by biopsy include the nephritis of anaphylactoid purpura, Goodpasture's syndrome, some of the collagen diseases, and some cases of nephrotic syndrome.

Baehr (1926) described a condition he called a

benign, curable form of haemorrhagic nephritis. The young adults in his report had recurrent or persistent haematuria with none of the other features associated with chronic nephritis. Some had bouts of gross haematuria, often precipitated by an acute infection of the upper respiratory tract, and either normal urine or microscopical haematuria detected between attacks. Others had microscopical haematuria which tended to persist. No tissue was studied pathologically, and though he believed the process was benign, the patients were not observed for a long period. Some of the children in the present study placed originally in Group 1 certainly fulfilled Baehr's description of haemorrhagic nephritis. Focal lesions were demonstrated on renal biopsy, and at this time 5 years later, 50% of these children have no evidence of renal disease. The experience of Livaditis and Ericsson (1962), who dealt with similar cases clinically but made no tissue evaluation, leads one to believe that the eventual prognosis is good: 36 of 50 children whom they observed for periods ranging from 4 months to 9 years were well and had no haematuria.

After 5 years, 50% of the children evaluated by us have persistent disease. These children were apt to have persistent haematuria from the onset associated with proteinuria. The renal histological abnormalities in the original biopsy specimen were more impressive in this group than in those who recovered. The duration of haematuria alone since onset of the disease has been impressive. Some of the children have hereditary haemorrhagic nephritis (Alport, 1927; Perkoff, 1967): this disease should be considered in any persons having recurrent or persistent haematuria. Early appearance of haematuria, proteinuria, and cylindruria, in a boy with a family history of haematuria or nephritis, in whom the episodes of haematuria seem to be triggered by infection of the upper respiratory tract, and with persistent microscopical haematuria between bouts of gross haematuria, should make one suspect this condition, in which histologically an initial focal glomerulonephritis will eventually develop into a generalized lesion.

A few patients with recurrent bouts of haematuria may have what McConville, West, and McAdams (1966) called familial benign haematuria. They noted a positive family history in 60% of their children with haematuria. Renal biopsy showed minimal change in 10 of their 17 patients so studied, and mesangial proliferation in one patient. It was their impression that the families did not have hereditary nephritis, but rather a mild, non-progressive, inherited condition. In their patients,

serum β_{1C} -globulin levels were normal despite active bleeding. This would be evidence against a smouldering type of hypocomplementaemic nephritis which might be manifested by haematuria (Feldman, Mardiney, and Shuler, 1966; West *et al.*, 1965). Proteinuria was not a significant abnormality in their cases. There seems to be a discrepancy between their patients and those in this report who have persistent disease; 'Hemastix' evaluation of relatives of their cases revealed more affected family members, but this was not so in our cases.

Retrospectively, antibiotics seem to have no effect on the disease. Almost all types of orally-administered antibiotics have been used. Steroids have been given to several patients but apparently without benefit.

Summary and Conclusions

Twenty-eight of 36 patients with recurrent haematuria who had renal biopsy 5 years previously were reassessed. 50% of those seen had had no haematuria for the past 18 months. None had hypertension, raised blood urea, decreased creatinine clearances, or signs of renal impairment. Neither the use of steroids nor antibiotics correlated with the cessation of haematuria. Males who initially had persistent microscopical haematuria between attacks of gross haematuria were more likely to be still having symptoms. 6 patients had a second renal biopsy. In one in which the haematuria had ceased there was a diffuse glomerulonephritis, but in the other 5 there was little change from the initial biopsy. Comparisons are drawn between this group with recurring haematuria and patients with glomerulonephritis and anaphylactoid purpura studied at the same time.

The final outcome of patients with recurrent bouts of gross haematuria will vary despite the initial similarity in clinical presentation and histopathology. Focal glomerulonephritis has multiple causes. In some children, the condition is reversible. In others, though haematuria persists,

the course is benign and non-progressive. The immediate prognosis is therefore usually good, but the ultimate prognosis is poor in the few who have familial progressive glomerulonephritis. Careful evaluation of case material, periodic functional evaluation of the patient, serial renal biopsy, and periodic observation of the patient over a long period is needed to provide a more complete natural history of this group of diseases.

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