studied with an electron microscope, neither by the examination of a single individual may such concepts as normal height or blood pressure, the prevalence of disease, herd immunity, the definition of subgroups vulnerable to certain diseases, differential survival, and prognosis be studied. This is the world of Galton and Snow, Farr and Graunt; the world to which Fisher, Ryle, and Bradford Hill have contributed so much in this century. It includes not only epidemiology but the scientific basis of prognostication, and some of the techniques used in the assessment of the effectiveness of prevention and treatment.

As it is my own personal interest I would be embarrassed to have to argue the importance of population medicine in the curriculum. I hope it is now a respectable science which can argue its own case. I would simply say this: that when the medical student is introduced to the study of man at the cellular and personal level he should at the same time be introduced to the group as a unit. He must learn to think in terms of populations and groups with the same facility as he thinks about the structure function and diseases of the individual.

Population medicine of course bears a close relationship to the other current of thought, to community care, particularly in the unique British system which fortunately gives to each general practioner a more or less definable population at risk for whose health he is responsible. As populations are the basic unit for this discipline, so information about people healthy and sick is its stock-in-trade. A modern medical school must therefore be associated with definable populations which it can sample and study, and create for itself efficient systems of medical information. This is one of the reasons why, with generous help, we have created a chair of medical information science in the formative period of the medical school.

Conclusions

From all this I draw the following conclusions.

Firstly, the place of the medical school remains, as always, squarely within the university. Indeed, there are indications that in the next decades the medical school will draw more widely on the skills of the university than it has ever done before. It will draw nourishment not only from science but from engineering, the social sciences, economics, law, and philosophy, and to each of these we hope it will contribute the stimulus of ideas. Juxtaposition alone will not guarantee the establishment of a free flow of ideas between medicine and the other faculties. A deliberate effort must be made to foster the appropriate type of relationship with each faculty.

Secondly, the administrative and managerial problems of medical schools, and in particular the reconciliation of the functions of teaching and research with service needs, require a major independent investigation. May I suggest that such a study might usefully be initiated by one of the charitable foundations?

Thirdly, a medical school can no longer reasonably be considered to consist of a faculty of medicine in a university and a teaching hospital and its satellites. In addition a substantial part of the resources of the school should be devoted to introducing the undergraduate to medicine outside the hospital. This requires capital for building and revenue for staff. The reorganization of the National Health Service which is shortly to take place would be a suitable occasion formally to recognize this fact and to lay a statutory duty on the proposed area health boards to provide facilities in the community, just as a similar duty is currently laid on boards of governors and regional hospital boards to provide facilities in hospital. Such formal recognition is not intended as a device to force co-operation. This is always forthcoming. It is to give public recognition in an unmistakable manner to the essential part which must be played by the community medical services in undergraduate education in the future.

My fourth and final conclusion can be expressed very briefly. It is that the modern medical school has a duty to study, to criticize, and to experiment with the system of medical care in which it operates.

References

Bishop, J. M. (1967). Inaugural Lecture in the University of Birmingham, "Doctors for Tomorrow."

Burnet, Sir Macfarlane (1953). *Lancet*, **1**, 103.

Flexner, A. (1930). *Universities, American, English, and German*. London, Oxford University Press.

General Medical Council (1967). *Recommendations as to Basic Medical Education*. London, G.M.C.

Gillie, Dame Annis (1970). In *Medicine an Outline for the Intending Student*, ed. E. D. Acheson. London, Routledge and Kegan Paul. To be published.

Himsworth, Sir H. (1969). *British Medical Journal*, **4**, 517.

McKeown, T. (1965). *Medicine in Modern Society*. London, Allen and Unwin.

Ministry of Health (1967). *Report on the Organization of Medical Work in Hospitals*. London, H.M.S.O.

Peart, S. (1970). Presidential address to the Section of Experimental Medicine. To be published in the *Proceedings of the Royal Society of Medicine*.

Vickers, Sir Geoffrey (1967). *Lancet*, **1**, 944.

Symptomless Haematuria in Childhood

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Summary: The clinical, laboratory, and renal biopsy findings in 47 children with symptomless haematuria are reported. In 41 the haematuria was recurrent. Local causes were excluded by means of intravenous urography, which was normal in all but one child, who had a horseshoe kidney.

Since all the patients had presented in a similar manner they were classified into four groups according to the severity of glomerular changes on renal biopsy. In group 1 the glomeruli were optically normal. In group 2 they showed a variable degree of mesangial thickening with absent or minimal cellular proliferation. In group 3 there was diffuse mesangial thickening and proliferation—an appearance indistinguishable from that of subsiding post-streptococcal glomerulonephritis. Compared with groups 1 and 2, more patients in this group had persistent proteinuria, as well as evidence of streptococcal infection preceding the initial haematuria. Only two patients showed severe proliferative glomerulonephritis on biopsy (group 4); both had heavy proteinuria and one repeatedly had low serum β1c-globulin levels.

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While the persistence of proteinuria between attacks of haematuria was found to be a fairly good indication of proliferative glomerulonephritis, creatinine clearances were mostly normal and did not correlate with the severity of glomerular abnormalities. Renal biopsy thus appears to be the most reliable means of distinguishing severe from mild changes.

Introduction

Symptomless haematuria in childhood continues to present a diagnostic problem to the clinician. Children with this complaint are commonly referred for urological investigations, when cystoscopic examination may give negative results and the label "focal nephritis" is likely to be attached. In this paper we present the clinical, laboratory, and histological findings in 47 children with symptomless haematuria and discuss the role of percutaneous renal biopsy. Our findings indicate that *focal* proliferative glomerulonephritis is a rare cause of this syndrome, and we present evidence that some patients may be suffering from an atypical form of post-streptococcal nephritis.

Patients and Methods

Symptomless haematuria is defined as the appearance of blood in the urine, visible to the naked eye, in the absence of dysuria, oliguria, oedema, or any other symptom suggesting renal disease. We have performed percutaneous renal biopsies on 52 children with this symptom. Five had either a family history of nephritis or were deaf, or both, and are excluded. Of the 47 included, six were referred direct by their family doctors, while another (Case 18) was found to have microscopical haematuria during the course of a school screening programme (Meadow *et al.*, 1969), and had his only attack of visible haematuria six weeks later. Fourteen children were already under the care of other consultants at the Birmingham Children's Hospital and the remaining 26 at other centres; they were referred specifically for renal biopsy. "Local" causes such as hydronephrosis. Wilms's tumour, calculus, and chronic pyelonephritis were excluded in all cases by means of intravenous urography. One boy had a horseshoe kidney, but this was not considered a primary cause of his haematuria.

All but six of the children were referred to us after more than one attack of haematuria, and many of them after numerous episodes; unfortunately, no uniform set of investigations had been carried out at the time of the first episode. Cystoscopy had been performed in 18 children with negative results. The integrity of the blood coagulation mechanism was shown in every instance before renal biopsy by normal prothrombin, partial thromboplastin and bleeding times and a normal platelet count. No patient was hypertensive, and all were found to have normal blood urea levels.

Creatinine clearance estimations were carried out in all but two patients by standard autoanalyser technique, on urine samples voided over a timed period of three to six hours during a water-induced diuresis; in most instances two consecutive three-hour collections were made and the results are presented as the mean of the two determinations. If the two results differed from each other by more than 20% they were discarded and the test repeated. Serum C'3 (β^1c-β1a-globulin) levels were measured in 26 recently investigated children by the technique of single radial immunodiffusion (Mancini *et al.*, 1965), purified antiserum being used. In five patients with sufficient proteinuria the selectivity was determined immunochemically by the method described by Joachim *et al.* (1964). Percutaneous renal biopsy was performed by our standard method (White, 1963). Specimens obtained before January 1968 were fixed in 10% formol-saline, and since that time in Bouin's alcoholic solution for five to six hours, followed by formalin post-fixation; all were paraffin-embedded, sectioned at 2-3μ, and stained with haematoxylin and eosin (H. & E.), periodic-acid-Schiff (P.A.S.), and periodic-acid-silver-methenamine (P.A.S.M.). In 28 instances 1-mm. cubes of presumed cortical tissue were first removed for electron microscopy. The tissue was fixed in 5% glutaraldehyde, post-osmicated, and embedded in Epon; ultrathin sections were doubly stained with uranyl acetate and lead citrate.

Renal Morphology

The patients have been divided into four groups according to the renal biopsy findings.

Group 1: Normal Glomeruli or Minor Abnormalities (17 Patients).—On renal biopsy most glomeruli showed no conspicuous abnormality (Fig. 1), though there was occasionally a slight localized increase of mesangial matrix. The tubules and interstitial tissue were normal. On electron-microscopical examination glomeruli seen in specimens from six patients failed to show any appreciable alteration in normal architecture. There was neither fusion of epithelial cell foot processes nor thickening of the endothelial cytoplasm lining the loops.

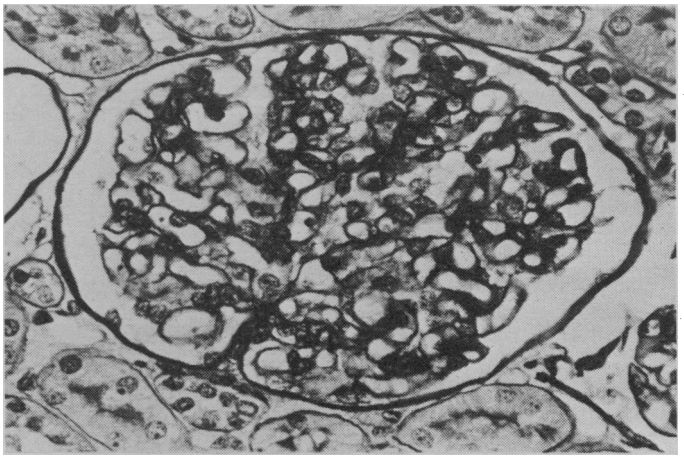

FIG. 1.—Representative glomerulus from Case 3 (group 1), showing no increase of mesangial matrix or cells. (P.A.S. × 415.)

Group 2: Mesangial Thickening without Proliferation (20 Patients).—The characteristic feature of this group was the increased amount of P.A.S.- and P.A.S.M.-positive fibrillar material in the mesangial areas of the glomerular tufts (Fig.

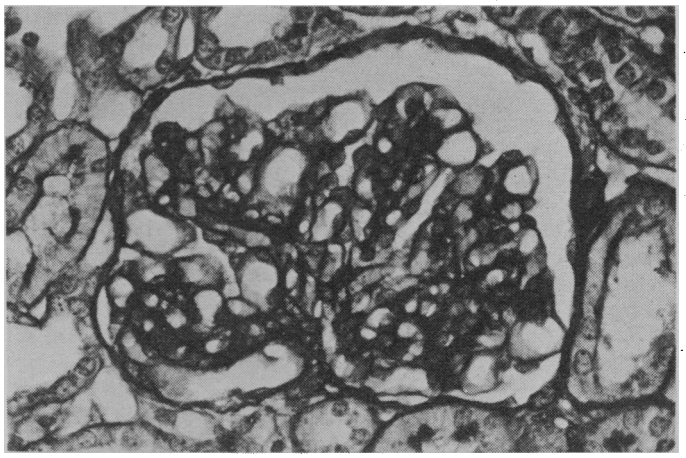

FIG. 2.—This glomerulus from Case 22 (group 2) shows an obvious increase of mesangial matrix without hypercellularity. (P.A.S. × 415.)

2). While this increase was regularly disposed throughout the lobular stalks, hypercellularity was inconspicuous, affecting only occasional glomeruli locally. On electron microscopy nine specimens contained glomeruli, and in them the increase of mesangial matrix was seen to be composed of both basement membrane-like material and mesangial cytoplasm. Some loops showed hypertrophy of the endothelial cytoplasm and irregular thickening of the basement membranes, though this was not apparent on optical microscopy. No electron-dense deposits were seen, nor was there any fusion of epithelial foot processes.

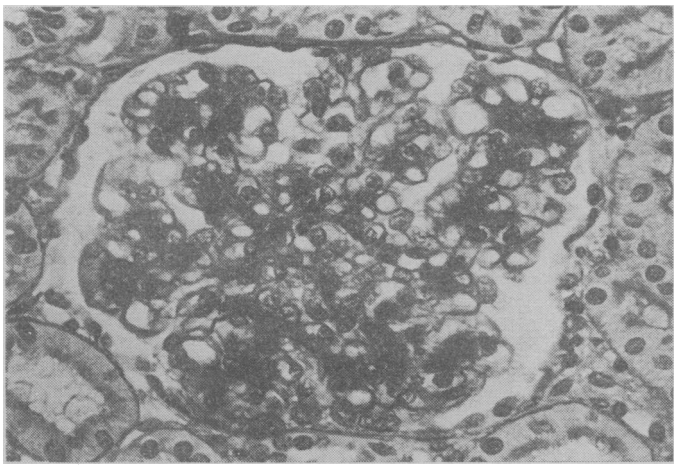

FIG. 3.—Glomerulus from Case 41, showing changes typical of group 3. There is diffuse proliferation of mesangial cells accompanied by an increase of matrix. (P.A.S. × 415.)

Group 3.—Mesangial Thickening with Proliferation (8 Patients).—All the glomeruli showed an obvious increase in P.A.S.-positive material throughout the mesangium, together with diffuse and predominantly mesangial hypercellularity (Fig. 3). Slight localized thickening of capillary walls was noticed in the P.A.S.-stained sections but the lumens were widely patent. Glomeruli from six patients examined electron-microscopically showed not only a greater increase of the mesangial matrix than was observed in group 2, but also an increased number of mesangial cells. Though the capillary basement membrane showed areas of both moderate thickening and extreme thinning (Fig. 4), the endothelial cytoplasm was very hypertrophic and thus contributed to the thickening

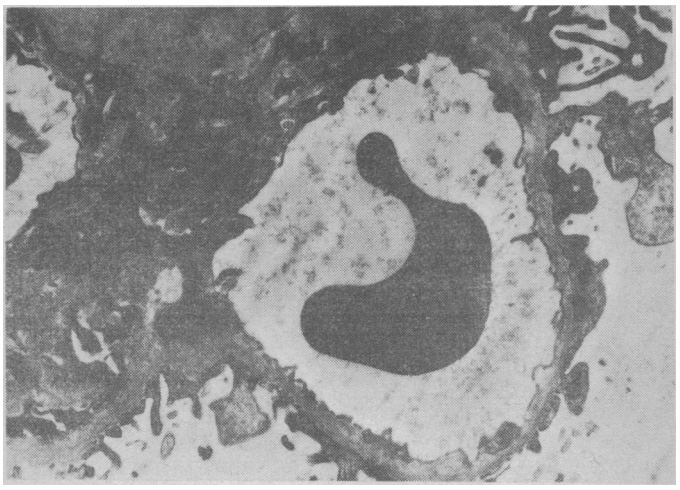

FIG. 4.—An electron micrograph of part of a glomerulus from Case 43 (group 3), illustrating both pronounced thinning and moderate thickening of the basement membrane, with fusion of some of the foot processes. (×7,300.)

seen locally on light microscopy. Fusion of foot processes adjacent to thickened basement membranes was seen in some cases, but this was not a consistent feature of the group.

Group 4.—Severe Proliferative Glomerulonephritis (2 Patients).—In Case 46 the glomeruli showed both diffuse mesangial proliferation and pronounced capillary wall thickening—features typical of membranoproliferative glomerulonephritis (Ogg *et al.*, 1968). On electron microscopy the thickening of the capillary walls was seen to be due to a number of factors, including fusion of foot processes, an irregular increase in the thickness of the lamina densa of the basement membrane, and many layers of basement membrane-like material lying between the basement membrane and the endothelium, which itself was thickened. The mesangium showed a great increase of matrix in addition to numerous proliferating cells. Case 47 showed on biopsy diffuse proliferative glomerulonephritis, though in a few glomeruli the proliferation was not prominent. Epithelial crescents were present in more than half of the glomeruli and there was some glomerular sclerosis. No tissue was available for electron microscopy. Though these two patients differed from one another in their glomerular morphology, it was felt justified to group them together since they both differed from patients in group 3 on account of the presence of either capillary wall thickening or epithelial crescents.

Clinicopathological Correlations

The main clinical and laboratory findings of the 47 patients are given in Table 1. Boys outnumbered girls except in group 4, in which both patients were girls. The age of onset and duration of illness at the time of biopsy were similarly distributed in all groups.

Upper respiratory infection preceded the first attack of haematuria more often in patients in group 3 (Table II). The incidence of preceding streptococcal infection, as judged by the finding of group A β-haemolytic streptococci in throat swab culture or an antistreptolysin-O (A.S.O.) titre greater than 200 units/ml., or both, was also somewhat higher in group 3 patients. These investigations, however, had been carried out in only half of the children in groups 1 and 2, and we hesitate to draw firm conclusions from such small numbers.

All except six children had recurrent attacks of haematuria, the frequency of which varied considerably. Of the patients whose urine had been adequately examined in the intervals, most showed persistent microscopical haematuria, though with greater frequency in groups 3 and 4. From Table II it can be seen that persistent proteinuria was observed much more often in groups 3 and 4. The proteinuria selectivity was measured in Cases 18, 35, 39, 43, and 46, and was impaired in all cases, regardless of glomerular morphology, the angle θ ranging from 51 to 66°.

Serum C'3 levels were reduced in three patients; surprisingly, two were in group 2 (Cases 24 and 31). Repeat determinations, however, have recently given normal levels—103 mg./100 ml. (Case 24) and 91 mg./100 ml. (Case 31). The other patient was in group 4 (Case 46), and has had persistently low levels for more than two years. Creatinine clearances show no correlation with glomerular morphology; a minority of patients in each group had clearances slightly below 80 ml./min./1·73 sq. m., our lower normal limit.

Discussion

Clinically the 45 patients in groups 1-3 appear to have the syndrome which in the past has been variously described as "essential" (Wyllie, 1955; Livaditis and Ericsson, 1962), "idiopathic" (Travis *et al.*, 1962), and "benign recurrent"

TABLE I.—*Clinical and Laboratory Findings in 47 Children with Symptomless Haematuria**

Case No.	Sex	At First Attack				No. or Frequency of Attacks	Persistent Microscopical Haematuria	At Time of Renal Biopsy				
		Age (years)	Preceding U.R.T.I.	A.S.O. Titre (units/ml.)	Throat Swab†			Duration of Symptoms	Serum C'3 (mg./100 ml.)	Creatinine Clearance (ml./min./ 1·73 sq. m.)	Proteinuria mg./ 100 ml.	Proteinuria mg./ 24 hours
						Group 1—17 Patients						
1	M	4½	–	250	0	1	0	1 week	–	–	0	–
2	F	10½	0	50	0	Daily	+	1 month	–	95	35	–
3	M	9½	0	160	0	5	0	3 months	–	92	0	–
4	M	11½	0	256	–	Many	–	4 months	202	61	100	546
5	F	9½	+	800	0	4	0	4 months	117	103	0	–
6	M	12½	–	–	0	1–2 per week	–	6 months	194	85	15	80
7	M	2½	+	625	+	2	0	6 months	–	74	0	–
8	M	11	0	–	–	3	+	6 months	141	139	35	273
9	F	10	0	–	–	3	–	6 months	–	–	0	–
10	M	10½	0	–	–	10	0	8 months	121	80	38	280
11	F	2	0	–	–	Several	–	9 months	–	118	20	–
12	M	5½	+	–	–	2	+‡	10 months (4½ years)	100	106	10	–
13	M	5	+	–	–	Monthly	–	1½ years	–	80	0	–
14	M	5	0	–	0	4	+	1½ years	–	73	0	–
15	M	3	+	–	0	Many	+	3 years	119	80	60	300
16	F	2	0	–	–	Many	+	3 years	–	74	0	–
17	F	5	+	–	–	Many	–	5 years	–	80	0	–
						Group 2—20 Patients						
18	M	16	+	250	0	1	+‡	2 days (6 weeks)	103	139	175	1,300
19	M	10	0	625	0	1	0	2 weeks	132	89	<10	–
20	M	5½	0	320	0	1	+	4 weeks	154	142	0	–
21	F	7½	0	100	0	3	0	2 months	105	78	0	–
22	M	4½	0	50	–	2	0	3 months	118	101	30	84
23	M	13½	+	200	0	1	+	6 months	92	119	0	–
24	M	5	0	–	–	Daily for 3 weeks	+	6 months	55	122	0	–
25	M	14	+	400	–	6	+	6 months	136	77	0	–
26	M	7½	+	800	–	2	+	6 months	–	118	0	–
27	M	11	0	50	–	Many	+	6 months	119	58	0	–
28	F	4½	0	–	0	Many	+	9 months	–	70	20	–
29	M	8½	0	–	–	2–3 per week	+	9 months	–	189	<10	–
30	M	4½	+	–	–	Monthly	0	9 months	–	94	10	–
31	M	4½	+	–	–	Weekly	–	1 year	24	86	50	214
32	M	7½	0	–	–	Several	+	1 year	110	104	0	–
33	F	4½	+	–	–	Several	+	2 years	110	118	10	63
34	F	6	+	–	0	5	0	2 years	–	75	10	–
35	M	3	+	–	–	Many	–	3 years	123	130	300	1,100
36	M	6	+	–	–	3–4 per year	+	4 years	–	90	20	–
37	M	6½	+	–	–	5	+	5½ years	–	81	0	–
						Group 3—8 Patients						
38	M	7	+	1,250	0	1	0	1 week	–	81	20	126
39	F	6	0	333	0	Daily for 6 weeks	+	6 weeks	137	95	160	1,400
40	M	5½	+	–	–	4	+	6 months	136	66	20	–
41	M	8½	+	250	+	3	+	9 months	113	104	20	90
42	M	8½	+	–	+	Several	+	1 year	180	99	0	–
43	M	2	+	–	0	6 per year	+	1½ years	109	102	150	375
44	M	8½	+	–	+	3	+	2½ years	–	106	15	253
45	F	6	+	–	0	4	+	3 years	–	108	400	2,000
						Group 4—2 Patients						
46	F	5	+	140	0	3–4 per year	+	4½ years	6	95	800	7,100
47	F	1½	0	50	–	Many	+	2½ years	–	74	300	–

*In each group cases are arranged according to duration of symptoms at the time of biopsy. + = present; 0 = none; – = information not recorded. †Only results of culture for group A β-haemolytic streptococci are given. ‡Microscopical haematuria was detected before the first attack of visible haematuria; the duration from the first abnormal urinalysis to biopsy is given in parentheses.

TABLE II.—*Comparative Incidence of Preceding Upper Respiratory Tract Infection (U.R.T.I.) and Group A β-Haemolytic Streptococcal Infection at Onset, and of Significant Proteinuria at the Time of Biopsy, in Groups 1-4**

	Group 1	Group 2	Group 3	Group 4
Preceding U.R.T.I.	6/15	11/20	7/8	1/2
Streptococcal infection†	4/9	5/11	5/7	0/2
Significant proteinuria‡	5/17	3/20	6/8	2/2

*In each column the figures indicate the number of positive results and the total number in which the data were recorded, respectively. †Derived from positive throat culture and/or A.S.O titre >200 units/ml. ‡Proteinuria >100 mg./24 hours, or >30 mg./100 ml. if the 24-hour output was not measured.

haematuria (Ayoub and Vernier, 1965). This syndrome was described in young adults by Baehr (1926), who emphasized its harmless nature. Follow-up studies ranging from 2 to 31 years (Wyllie, 1955; Ross, 1960; Ayoub and Vernier, 1965; Todd and Bouton, 1966; Singer *et al.*, 1968; Johnston and Shuler, 1969) show general agreement regarding the good prognosis ascribed to the syndrome.

The patients studied, however, do not appear to form a homogeneous group, for histological descriptions of glomerular changes observed in renal biopsy specimens during the past decade vary appreciably. This may be at least partly due to the subjective nature of histological interpretation and lack of uniform nomenclature; the manner in which pathological terms are used by individual writers can be appraised only on reference to the illustrations accompanying their articles. Those by Ross (1960), Lannigan and Insley (1965), and Bodian *et al.* (1965) show hypercellularity and mesangial thickening of a degree sufficient to warrant the description "proliferative glomerulonephritis." On the other hand, most of the biopsies reported by Ayoub and Vernier (1965), McConville *et al.* (1966), and Singer *et al.* (1968) showed no abnormality, though some contained glomeruli showing minimal focal hypercellularity. Equally inconspicuous abnormalities, consisting of clusters of four or five mesangial cells in occasional glomeruli, were observed by Ferris *et al.* (1967), but were referred to as "focal glomerulitis."

Meaning of Focal Glomerulonephritis

According to Baehr (1926) the term "focal nephritis" was originally used by Volhard and Fahr (1914) as a clinical diagnosis to describe patients in whom an attack of haematuria occurred at the height of a respiratory infection. From a retrospective analysis of 365 children diagnosed as having acute nephritis, however, Payne and Illingworth (1940) were unable to detect any clear-cut differences in either renal function or prognosis between patients with oedema at onset and those with haematuria alone, and they remained unconvinced that "focal nephritis" was an entity. Nevertheless, this term has for many years remained a fashionable clinical label for patients

with symptomless haematuria. Heptinstall and Joekes (1959), however, used the term "focal glomerulonephritis" in a strictly pathological sense and encountered 13 examples in a series of 100 consecutive renal biopsy specimens. These were obtained from adult patients with systemic lupus erythematosus, polyarteritis nodosa, Henoch-Schönlein purpura, and the nephrotic syndrome.

Focal glomerulonephritis has also been reported in Goodpasture's syndrome (Rusby and Wilson, 1960). Similarly West *et al.* (1968) found that 11 children with focal glomerulonephritis presented clinically with the nephrotic syndrome accompanied by haematuria. Thus, all these patients showed, in addition to haematuria and proteinuria, a variety of clinical manifestations including oedema, hypertension, and nitrogen retention, in contrast to their absence in the children we have described. With the histological criteria stated by Heptinstall and Joekes (1959), *none* of our patients can be said to have focal glomerulonephritis. We endorse the plea by Lannigan and Insley (1965) to restrict the use of this term to the description of renal morphological changes and suggest that the *clinical* syndrome should be called "symptomless" or "recurrent" haematuria.

Familial nephritis is usually recognized by virtue of the occurrence of overt nephritic manifestations in relatives; however, McConville *et al.*, (1966) found microscopical haematuria on routine testing in relatives of 10 out of 17 children with apparently non-familial haematuria. Arneil *et al.* (1969) subsequently screened 70 close relatives of 17 children with recurrent haematuria but found microscopical haematuria in the mother and two half-sisters of only one child. We have so far tested all the first-degree relatives of 18 patients in groups 1-3, with negative results except in the mother of Case 8. The familial cases described by McConville *et al.* (1966) seem to differ from other forms of hereditary nephritis such as Alport's syndrome (White *et al.*, 1964) in their normal renal histology, benign course, and lack of overt nephritis or deafness in relatives. Though the relatives with occult haematuria have not been investigated by renal biopsy, it seems probable that they would show the same range of histological changes as our patients with macroscopical haematuria. Similar changes were noted in biopsy specimens obtained from four apparently healthy schoolchildren found to have microscopical haematuria on screening (Meadow *et al.*, 1969). One of them (included here as Case 18) fortuitously had an attack of visible haematuria on the day of admission to hospital for renal biopsy, six weeks after the initial urinalysis, and still had microscopical haematuria one year later.

Four Groups

The patients whom we investigated resembled one another clinically in their freedom from symptoms and signs other than macroscopical haematuria. Since renal biopsy was performed on all 47 children, the glomerular morphological characteristics appeared to us to form a logical basis for subdivision. Though for convenience we separated them into four categories we would emphasize that there was no sharp division between groups 1 and 2; indeed we experienced difficulty in placing occasional biopsy specimen sections. The range of appearances encompassed by these two groups is comparable with what we would call "minimal changes" in biopsy specimens obtained from children with the nephrotic syndrome.

In group 3, on the other hand, the mesangial thickening and hypercellularity were diffuse, justifying a pathological diagnosis of mesangial proliferative glomerulonephritis. Similar abnormalities were described in detail by Jennings and Earle (1961) in adult patients with subsiding or early chronic post-streptococcal glomerulonephritis, and have since been reported in children recovering from post-streptococcal nephritis (Hutt and White, 1964; Dodge *et al.*, 1968). The same appearances were subsequently described in adults (Lawrence *et al.*, 1963) and children (White, 1967) with the nephrotic syndrome. It is not clear whether patients showing this appearance on renal biopsy are all atypical examples of post-streptococcal nephritis, possibly silent at onset (White, 1964), or whether the lesion represents a non-specific glomerular response to a variety of stimuli.

On electron microscopy discrete subepithelial deposits ("humps") extending from the basement membrane are considered pathognomonic of post-streptococcal glomerulonephritis in both adults (Osawa *et al.*, 1966; Herdson *et al.*, 1966) and children (Dodge *et al.*, 1968); they are seen characteristically during the first six weeks of illness, though very occasional humps have been reported in the later stages of this condition (Dodge *et al.*, 1968). While we have frequently identified humps in biopsy specimens obtained from children during the acute phase of post-streptococcal glomerulonephritis, both by electron microscopy, and more recently by optical microscopy using ultrathin (0·5μ) silver-stained sections (Movat, 1961) or a chromatrope-P.A.S.M. method (T. Ehrenreich and T. Espinosa, personal communication, 1967), we failed to find them in any of our patients with symptomless haematuria, despite a careful search. In this respect our findings differ from those of Singer *et al.* (1968), who claimed to have observed humps in 11 out of 31 children with recurrent haematuria of more than three months' duration, as well as in children with healing post-streptococcal glomerulonephritis as long as four years after onset. Our failure to identify humps in the group 3 biopsy specimens, however, does not preclude the possibility of a streptococcal aetiology. Our main finding on electron-microscopical examination was a striking variation in thickness of the capillary basement membranes, from being extremely thin to slightly thickened within the same loop, particularly in groups 2 and 3. This was also observed by Lannigan and Insley (1965) and Singer *et al.* (1968), though the latter workers regarded it as a normal variant.

Distinguishing Features

A number of features distinguish the patients in group 3 from those in groups 1 and 2 (Table II). The greater frequency of preceding upper respiratory infections, the marginally greater incidence of β-haemolytic streptococcal infection, and the more striking proteinuria, in addition to the mesangial proliferation observed in renal biopsy specimens, suggest that group 3 might represent an atypical form of post-streptococcal nephritis. Ayoub and Vernier (1965) also found evidence of group A β-haemolytic streptococcal infection in 7 out of 16 children (44%) with recurrent haematuria. They argued, however, that this might represent no more than the streptococcal carrier rate for the age group involved, though they thought that the possibility of previous post-streptococcal nephritis was supported by the observation that three out of the five patients whose biopsies showed focal proliferative changes had raised streptococcal antibody titres. On the other hand, it is well known that in patients with typical post-streptococcal nephritis subsequent attacks of haematuria may sometimes be provoked by upper respiratory infections, as illustrated by three patients of Bodian *et al.* (1965) and one of Lannigan and Insley (1965).

We have also considered the possibility that the changes observed in groups 1-3 may represent different stages in the evolution of a single nephropathy. Of the children reported by Arneil *et al.* (1969) to have an increase of P.A.S.-positive material in the axial (mesangial) regions of their glomeruli, two had shown mild proliferative glomerulonephritis in previous biopsies. We have not yet, however, performed repeat biopsies on sufficient of our patients to draw any conclusions regarding the evolution of the glomerular lesions. If spontaneous progression were to occur from group 1 towards

group 3, or regression from group 3 towards group 1, one might expect to find a relation between the histological appearance and the duration of symptoms, but Table I shows that there is no such correlation.

The two patients in group 4 (Cases 46 and 47) were included in this series because of their clinical resemblance to the remaining patients, but were placed in a separate group owing to the obviously greater severity of the lesions found on renal biopsy. Case 46 has had persistently low levels of β_{1c}-globulin, in keeping with the diagnosis of membranoproliferative glomerulonephritis (Ogg *et al.*, 1968). A further example of this condition presenting with recurrent haematuria was reported by Arneil *et al.* (1969). This boy subsequently developed the nephrotic syndrome, and investigations showed a low serum C'3 level, together with "mixed membranous and proliferative lesions" on biopsy.

It is noteworthy that both normal and slightly reduced creatinine clearance figures were obtained in each of groups 1-4 (Table I), reflecting the lack of correlation between glomerular structure and function which Risdon *et al.* (1968) observed. The selectivity of proteinuria was impaired in all five patients in whom it was measured, regardless of glomerular morphology, and does not appear to possess the prognostic significance attributed to it in children with the nephrotic syndrome (Cameron and White, 1965). We are unable to explain the initially low levels of serum C'3 obtained in Cases 24 and 31, though they are occasionally recorded in nephrotic patients with optically normal glomeruli (Ogg *et al.*, 1968).

Our findings unfortunately do not shed new light on the aetiology of recurrent haematuria beyond suggesting the possibility that some cases may be instances of atypical post-streptococcal glomerulonephritis, but they have enabled us to rationalize the investigation of patients. It seems that cystoscopy is not a useful investigation when intravenous urography is normal. Creatinine clearance and proteinuria selectivity determinations form part of the routine assessment but have little diagnostic or prognostic significance. Measurement of serum C'3 levels at any stage of the illness may on occasion lead to a diagnosis of membranoproliferative glomerulonephritis, as in Case 46, but might be more informative at the time of the first episode. If patients in group 3 represent atypical post-streptococcal nephritis, as we have suggested, they might be expected to have low levels at onset. As Ferris *et al.* (1967) also noted, it is evident from our investigations that proliferative glomerulonephritis will more often be diagnosed on renal biopsy when there is persistent proteinuria and that a severe lesion is unlikely to be diagnosed in its absence.

Thus renal biopsy appears to be the most satisfactory way of differentiating between mild and severe glomerular disease in patients with proteinuria. In those without proteinuria renal biopsy, though not essential for diagnostic purposes, may on occasion enable the paediatrician faced with anxious parents to prognosticate more confidently, with the knowledge that glomerular abnormalities are minimal. We reiterate Cameron's (1964) plea for the more frequent referral of patients during their first attack of haematuria, when comprehensive investigations, including a search for evidence of β-haemolytic streptococcal and other infections, as well as renal biopsy, would be more likely to increase our knowledge of the aetiology of this puzzling condition. Against this background a more complete picture of the evolution of the glomerular lesions could be constructed, as Johnston and Shuler (1969) suggested, by periodical assessment of renal function and a further renal biopsy after several years' interval.

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REFERENCES

Arneil, G. C., Lam, C. N., McDonald, A. M., and McDonald, M. (1969). *British Medical Journal*, **2**, 233.
Ayoub, E. M., and Vernier, R. L. (1965). *American Journal of Diseases of Children*, **109**, 217.
Baehr, G. (1926). *Journal of the American Medical Association*, **86**, 1001.
Bodian, M., Black, J. A., Kobavashi, N., Lake, B. D., and Shuler, S. E. (1965). *Quarterly Journal of Medicine*, **34**, 359.
Cameron, A. H. (1964). *Archives of Disease in Childhood*, **39**, 299.
Cameron, J. S., and White, R. H. R. (1965). *Lancet*, **1**, 463.
Dodge, W. F., Spargo, B. H., Bass, J. A., and Travis, L. B. (1968). *Medicine*, **47**, 227.
Ferris, T. F., Gorden, P., Kashgarian, M., and Epstein, F. H. (1967). *New England Journal of Medicine*, **276**, 770.
Heptinstall, R. H., and Joekes, A. M. (1959). *Quarterly Journal of Medicine*, **28**, 329.
Herdson, P. B., Jennings, R. B., and Earle, D. P. (1966). *Archives of Pathology*, **81**, 117.
Hutt, M. S. R., and White, R. H. R. (1964). *Archives of Disease in Childhood*, **39**, 313.
Jennings, R. B., and Earle, D. P. (1961). *Journal of Clinical Investigation*, **40**, 1525.
Joachim, G. R., Cameron, J. S., Schwartz, M., and Becker, E. L. (1964). *Journal of Clinical Investigation*, **43**, 2332.
Johnston, C., and Shuler, S. (1969). *Archives of Disease in Childhood*, **44**, 483.
Lannigan, R., and Insley, J. (1965). *Journal of Clinical Pathology*, **18**, 178.
Lawrence, J. R., Pollack, V. E., Pirani, C. L., and Kark, R. M. (1963). *Medicine*, **42**, 1.
Livaditis, A., and Ericsson, N. O. (1962). *Acta Paediatrica*, **51**, 630.
McConville, J. M., West, C. D., and McAdams, A. J. (1966). *Journal of Pediatrics*, **69**, 207.
Mancini, G., Carbonara, A. O., and Heremans, J. F. (1965). *Immunochemistry*, **2**, 235.
Meadow, S. R., White, R. H. R., and Johnston, N. M. (1969). *British Medical Journal*, **3**, 81.
Movat, H. Z. (1961). *American Journal of Clinical Pathology*, **35**, 528.
Ogg, C. S., Cameron, J. S., and White, R. H. R. (1968). *Lancet*, **2**, 78.
Osawa, G., Beres, J., and Kimmelstiel, P. (1966). *American Journal of Clinical Pathology*, **46**, 295.
Payne, W. W., and Illingworth, R. S. (1940). *Quarterly Journal of Medicine*, **9**, 37.
Risdon, R. A., Sloper, J. C., and de Wardener, H. E. (1968). *Lancet*, **2**, 363.
Ross, J. H. (1960). *Quarterly Journal of Medicine*, **29**, 391.
Rusby, N. L., and Wilson, C. (1960). *Quarterly Journal of Medicine*, **29**, 501.
Singer, D. B., Hill, L. L., Rosenberg, H. S., Marshall, J., and Swenson, R. (1968). *New England Journal of Medicine*, **279**, 7.
Todd, R. McL., and Bouton, M. J. (1966). *Proceedings of the Royal Society of Medicine*, **59**, 209.
Travis, L. B., Daeschner, C. W., Dodge, W. F., Hopps, H. C., and Rosenberg, H. S. (1962). *Journal of Pediatrics*, **60**, 24.
Volhard, F., and Fahr, T. (1914). *Die Brightsche Neirenkrankheit*. Springer, Berlin. Cited by Baehr (1926).
West, C. D., McAdams, A. J., and Northway, J. D. (1968). *Journal of Pediatrics*, **73**, 184.
White, R. H. R. (1963). *Archives of Disease in Childhood*, **38**, 260.
White, R. H. R. (1964). *Guy's Hospital Reports*, **113**, 190.
White, R. H. R. (1967). *Proceedings of the Royal Society of Medicine*, **60**, 1164.
White, R. H. R., Parsons, V., and Walt, F. P. (1964). *Guy's Hospital Reports*, **113**, 179.
Wyllie, G. G. (1955). *Proceedings of the Royal Society of Medicine*, **48**, 1113.