Personal practice

The investigation of haematuria

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Visible haematuria is a common presenting symptom of renal and urinary tract disease in children, and is often recurrent. Symptomless microscopic haematuria is not frequently detected on routine examination of the urine during coincidental illness or population screening. Most cases are found to be caused by primary glomerular disorders; however, surgically remediable causes are occasionally diagnosed, and it is mandatory that every child is appropriately investigated. Such an assessment should be tailored to the individual patient's particular circumstances and not carried out in a routine and perhaps needlessly invasive manner. It is best to proceed in planned steps, aimed first at confirming the presence of haematuria, then establishing the anatomical site of bleeding, and finally the diagnosis. A logical plan requires a knowledge of the causes, which are reviewed below.

Non-glomerular causes (table 1)

Bleeding from the genitalia, as in severe vulvovaginitis, gross sexual abuse, or vaginal foreign body may present with apparent haematuria, and careful inspection of the genitalia is an essential procedure. For the first menstrual period to be mistaken for haematuria is something which I have observed only once in more than 25 years. Bleeding from an anal fissure into a baby's nappy, where it may be diffused by urine, is a rare cause of difficulty.

Acute urinary tract infection may be accompanied by microscopic haematuria, but a clinical presentation with visible haematuria is unusual in children. Hypercalciuria has recently been reported as an occasional cause of persistent microscopic haematuria, and its correction by a liberal fluid intake together with the avoidance of a high dietary calcium intake or, if necessary, the use of diuretics, is usually curative.

Surgically remediable causes of haematuria include calculus, hydronephrosis, neoplasm, and trauma, and a suitable imaging procedure must be undertaken to exclude them. Causes of haematuria in the bladder are very rare during childhood, and cystoscopy is, almost without exception, a needless investigation. The ease of international travel means that today, however, some children living in temperate countries may previously have resided in tropical zones where the parasite Schistosoma haematobium is prevalent. Prompt treatment of schistosomiasis is essential if hydronephrosis due to fibrotic changes at the ureterovesical junction are to be avoided.

Other infrequent causes of haematuria include subacute bacterial endocarditis, sickle cell disease, tuberculosis, and renal cysts. Although adult polycystic disease is, today, increasingly diagnosed in childhood by ultrasound screening, haematuria rarely occurs before adulthood. The loin pain-haematuria syndrome, well described in young women, is rare in childhood; I have seen only two cases—a 15 year old girl and a 12 year old boy. The diagnosis eludes conventional imaging procedures and renal angiography is necessary in suspected cases. Haematuria may occasionally follow unusually strenuous and sustained exertion, usually in young adult males, although I have once seen it in a healthy 12 year old boy. Although urinary tract bleeding may complicate coagulation disorders, haematuria is almost never the presenting symptom.

Table 1 Non-glomerular causes of haematuria

<table>
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<tr>
<th>Causes</th>
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<tr>
<td>Genital or anal bleeding</td>
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<tr>
<td>Urinary tract infection</td>
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<td>Hypercalciuria</td>
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<tr>
<td>Calculus</td>
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<tr>
<td>Hydronephrosis</td>
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<tr>
<td>Neoplasm</td>
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<tr>
<td>Trauma</td>
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<tr>
<td>Schistosoma haematobium infection</td>
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<tr>
<td>Subacute bacterial endocarditis</td>
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<tr>
<td>Sickle cell disease</td>
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<tr>
<td>Tuberculosis</td>
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<tr>
<td>Renal cysts</td>
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<tr>
<td>Loin pain-haematuria syndrome</td>
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<tr>
<td>Blood coagulation disorder</td>
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Glomerular causes (table 2)

PROLIFERATIVE GLOMERULONEPHRITIS
In typical poststreptococcal glomerulonephritis of moderate severity, signs of salt and water retention are present, with hypertension, raised jugular venous pressure, clinical or radiological cardiomegaly, and minimal oedema. In mild cases, however, these features may be absent. The condition can only be diagnosed with confidence within one or two months of onset of haematuria, when the serum titres of streptococcal antibodies are raised and the serum complement C3 component is reduced but gradually returning to normal. Poststreptococcal nephritis is not a recurrent disorder, even though in severe cases it may be slow to heal, and the diagnosis need not be seriously entertained in a child who has had repeated attacks of macroscopic haematuria over a period of six months or more.

Although a nephrotic or nephritic presentation is the rule in mesangiocapillary glomerulonephritis, Cameron et al noted haematuria as the first symptom in 7% of cases.8 Persistent, heavy proteinuria is almost invariably present, however, and a low serum C3 concentration would be strongly suggestive while a normal concentration would not exclude the condition.9 Haematuria is the commonest renal manifestation of Henoch-Schönlein purpura.10 While recognition of the systemic features will obviate any diagnostic difficulty in the vast majority of cases, an occasional patient may present with symptomless haematuria months or even years after the initial illness has resolved; the diagnosis is then dependent on a careful history. This clinical pattern is of interest because of its similarity to that of IgA nephropathy, and the occurrence of mesangial IgA deposits in Henoch-Schönlein nephritis, together with a report of twin boys, one affected by Henoch-Schönlein nephritis and the other by IgA nephropathy,11 suggests that the two conditions may have a common immunopathological basis.

IGA NEPHROPATHY
IgA nephropathy is probably the commonest cause of recurrent, symptomless, macroscopic haematuria and persistent microscopic haematuria in children and young adults. Since its first description in 196812 a wealth of literature has been published and the subject is well reviewed by D'Amico.13 There is appreciable geographical variation in its incidence; it is commoner in southern than north western Europe and is particularly common in Japan and South East Asia. Estimates of its incidence will vary according to referral practice; since the screening of Japanese school children for urinary abnormalities was begun in 1974, IgA nephropathy has been the commonest form of primary glomerulopathy to be diagnosed in paediatric renal units.2 A low incidence has been reported in negroes; some workers have reported a significant association with HLA-DR4 antigens but others have failed to confirm this, and there are rare reports of siblings being affected.2

The light microscopic findings in renal biopsy specimens in children are generally minimal or consist of mild, focal, and segmental mesangial proliferation. A minority of children who have accompanying persistent proteinuria may later develop segmental glomerular sclerosis. The diagnosis is established by the finding, on immunofluorescence microscopy, of diffuse mesangial deposits of IgA, occasionally in isolation but more usually with IgG or C3, or both. On electron microscopy, dense deposits corresponding to these immune complexes are observed particularly in the perimesangial regions. The aetiology remains uncertain and it is still debated whether the mesangial deposits represent increased production and delivery or decreased clearance of IgA immune complexes.2 An interesting recent finding is the presence in a few patients of circulating antigliadin antibodies, coupled with flat mucosa on jejunal biopsy and clearance of haematuria in response to a gluten free diet,14 suggesting a possible connection between the relatively high prevalence of IgA nephropathy in Italy and the use of wheat based pasta as the staple diet.

The course of the illness is generally protracted, although not as often progressive as it is in adults. About one third of children lose their symptoms, but the remainder continue to have haematuria, if only microscopic, and no effective treatment has yet been found. A few children develop proteinuria, associated with segmental glomerular sclerosis, and are at risk of future chronic renal failure.2 IgA deposition is reported to recur in renal transplants, although the clinical manifestations are mild and renal function remains stable in the short term.15

THE ALPORT NEPHROPATHY
The next most common cause of glomerular haematuria in childhood is the Alport nephropathy. The
term Alport's syndrome should perhaps be confined to those families in which neurosensory deafness occurs in addition to nephritis, as originally described.\textsuperscript{16} Males more often exhibit deafness than females, and typically progress to chronic renal failure in early adulthood, whereas most females remain in apparently good health throughout life. In a few families deafness is absent, even in males, who survive to a greater age before developing chronic renal failure; these we have referred to as Alport variants.\textsuperscript{17} A variety of ocular defects have also been described\textsuperscript{18,19}; these include posterior polymorphous dystrophy of the cornea, anterior lenticonus, and perimacular flecks, all of which represent basement membrane defects. We have observed strong positive correlation between deafness, ocular abnormalities, proteinuria, and chronic renal failure.\textsuperscript{19,20}

Like IgA nephropathy, the Alport nephropathy is of geographically variable prevalence. This may reflect geographic differences, referral practices, and the morphological criteria used for diagnosis. The condition is diagnosed in specimens from renal biopsies undertaken in children with haematuria more than twice as frequently in Birmingham than in Manchester and Leeds,\textsuperscript{21,22} although the incidence of IgA nephropathy in all three centres is similar. The lack of reports of hereditary nephritis from Singapore suggest that it is uncommon in the Chinese, although we have diagnosed it in one such family in Birmingham. I have not yet seen it in a negro child and know of no published reports of its occurrence.

The inheritance of the Alport nephropathy may be heterogeneous, although most of the published pedigrees\textsuperscript{23} and all that we have studied in Birmingham\textsuperscript{20} are consistent with X linkage. It requires male to male inheritance to disprove X linked inheritance, and such instances are not only rare but also unsubstantiated by unequivocal ultrastructural diagnostic criteria. A family history of nephritis and deafness is not always obtained as female 'carriers' may have asymptomatic microscopic haematuria as their only clinical manifestation. It is therefore essential to test the urine of all first degree relatives of children presenting with haematuria before dismissing the disorder as non-familial; we have detected at least 10 affected families in this manner.\textsuperscript{21} Even then, haematuria in females may be intermittent, and a single negative test does not exclude the diagnosis.\textsuperscript{20} It is uncertain whether those rare cases diagnosed on firm morphological grounds in the absence of affected relatives are true mutants or the offspring of affected women who do not display clinical manifestations.\textsuperscript{17}

The genetics of the Alport nephropathy will ultimately be settled by means of DNA probes, and preliminary studies point strongly towards an abnormal gene on the X chromosome.\textsuperscript{24}

The changes seen on light microscopy of renal biopsy specimens are non-specific; segmental glomerulosclerosis and interstitial foam cells are not usually found in young children but develop as a prelude to declining renal function and correlate strongly with the presence of heavy proteinuria.\textsuperscript{17} Immunofluorescence is essentially negative. The hallmark of diagnosis lies in the characteristic ultrastructural alterations of the glomerular basement membrane.\textsuperscript{25-27} This consists of irregular thickening of the membrane, with complex replication of the lamina densa, the clear spaces between the layers containing electron dense aggregates, and has been likened to a basket weave.\textsuperscript{28} Although we have observed similar but strictly localised changes in a variety of other glomerulopathies, widespread glomerular basement membrane involvement is diagnostic of the Alport nephropathy.\textsuperscript{29} That this abnormality may be due to defective biochemical composition\textsuperscript{29} is supported by the absence from the glomerular basement membrane of the Goodpasture antigen.\textsuperscript{30}

'THIN MEMBRANE DISEASE'--AN ALPORT VARIANT?

In addition to thickening of the glomerular basement membrane attenuated segments may be seen.\textsuperscript{17} Occasionally they are so thin that the lamina densa becomes interrupted. Bernstein has suggested that this may be the primary lesion,\textsuperscript{31} and the observation by Habib \textit{et al} that this is the prevalent abnormality in younger children lends support to this concept.\textsuperscript{29} In some children with familial haematuria there is diffuse attenuation of the glomerular basement membrane.\textsuperscript{17} When originally described this was believed to be a benign condition,\textsuperscript{32} and this appears to be true in many cases. Chronic renal failure of late onset has, however, since been reported in relatives of four patients with thin membrane disease.\textsuperscript{29} I have recently biopsied two siblings with haematuria, the older of whom had classical changes of the glomerular basement membrane and the younger, a boy aged 18 months, diffuse attenuation only. Similar ultrastructural differences were reported in a mother and son, respectively, by Habib \textit{et al}.\textsuperscript{29}

The relationship between thin membrane disease and the Alport nephropathy is a complex one and requires further evaluation. We are currently undertaking morphometric measurements in an attempt to elucidate this problem, having first determined what we believe to be the normal range of thickness in the glomerular basement membrane in children with minimal change nephrotic syndrome.\textsuperscript{33} In the
meantime, a cautious prognosis must be given in children with familial haematuria who show thin membrane disease on renal biopsy.

MINOR GLOMERULAR ABNORMALITIES
A few children with persistent haematuria, in whom comprehensive investigation is normal, show little or no abnormality on renal biopsy, and appear to run a benign course. The reason for the haematuria remains unexplained. A few biopsy specimens show bright, immunofluorescent C3 staining of arterioles,34 the significance of which is uncertain. Like Habib et al.,29 however, we have also observed an ultrastructurally normal glomerular basement membrane in three children representing families with clinically typical Alport’s syndrome.28 One child has subsequently developed characteristic changes of the membrane in a repeat biopsy specimen, and clearly a normal result on biopsy in the presence of familial nephritis cannot necessarily be considered benign.

A management plan (table 3)

HISTORY AND PHYSICAL EXAMINATION
History taking should be directed towards symptoms such as frequency, dysuria, and loin pain: joint pains and rash; deafness in the child or family; a family history of renal disease; racial and geographical factors; and the possibility of exposure to tropical disorders. A note should be made of the child’s age; haematuria beginning before 5 years of age is more likely to be caused by hereditary nephritis than IgA nephropathy. A complete physical examination must always be performed; points requiring particularly attention are the presence of oedema, hypertension, raised jugular venous pressure, bruising or petechiae, joint swelling, renal masses, anal and genital inflammation, trauma, or bleeding. Any suggestion of deafness, from the history or examination, will require an audiogram for confirmation.

Urine examination
The initial task is to confirm the presence of haematuria, which is not invariably the cause of suggestive discoloration of the urine. For example, uric acid crystals deposited in a baby’s nappy impart a faint, pink tinge, which may be misinterpreted by a naturally anxious mother. Certain pigments, such as those contained in beetroot and eosiin used in boiled sweets, are said to cause red discoloration in certain individuals; rifampicin causes a bright orange colour which could be mistaken by the unwarly. Haemoglobinuria is rarely seen in white children, when it may be caused by cold agglutinins complicating mycoplasma pneumonia; it is an occasional complication of glucose-6-phosphate dehydrogenase deficiency in negroes living in regions where malaria caused by Plasmodium falciparum is prevalent.

Macroscopic haematuria imparts a characteristically smoky appearance to the urine; microscopic haematuria produces no change visible to the naked eye. Positive results from chemical strip tests (Hemastix, Labstix, etc) rely on haemolysis due to extremes of pH and osmolar change in the urine. Trace positive readings often occur in healthy subjects while ambulant, in the absence of haematuria detectable by microscopy, and I have occasionally observed negative results in association with minimal microscopic haematuria. It is therefore necessary to confirm the presence of haematuria by microscopy, and an inexpensive microscope should be regarded as an essential item of equipment for a renal clinic. It is also preferable, incidentally, to hold a renal clinic in the morning when the cellular (and bacterial) content of the urine is less likely to be influenced by dilution, and an early morning specimen collected by the patient at home for protein determination is still reasonably fresh.

Examination of the urine offers the opportunity to look for other abnormalities which may give a clue to the aetiology of the haematuria. Bacteriuria may be observed microscopically,35 but infection must be excluded by routine urine culture. A glomerular origin would be supported by the presence in the urine of granular casts. Erythrocytes which have passed through the glomerular capillary wall

Table 3 An initial management checklist

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<tr>
<th>Procedure</th>
<th>Possible findings</th>
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<td>History taking</td>
<td>Frequency and dysuria</td>
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<tr>
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<td>Loin pains, renal colic</td>
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<td>Joint pains, rash</td>
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<td>Bleeding tendency</td>
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<td>Deafness</td>
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<td>Family history</td>
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<td>Strenuous exertion</td>
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<td>Tropical exposure</td>
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<td>Examination</td>
<td>Oedema</td>
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<td>Hypertension</td>
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<td>Raised jugular venous pressure</td>
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<td>Purpura, joint swelling</td>
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<td>Renal mass</td>
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<td>Genital or anal bleeding</td>
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<td>Deafness</td>
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<tr>
<td>Urine examination</td>
<td>Pyuria, bacteriuria</td>
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<td></td>
<td>Granulat casts</td>
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<td></td>
<td>Dysmorphic erythrocytes</td>
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<td>Schistosoma haematobium</td>
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<td></td>
<td>Proteinuria</td>
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<td></td>
<td>Hypercalciuria</td>
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<tr>
<td>Imaging</td>
<td>Gross lesions</td>
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become misshapen and show appreciable variation in diameter. Birch et al reported that glomerular and lower tract haematuria could be reliably distinguished by phase contrast microscopy.36 I have not personally employed this technique, but long experience with conventional microscopy has taught me to recognise dysmorphic erythrocytes with reasonable confidence. Where there is a history of tropical exposure, centrifuged urine should be examined microscopically for the ova of Schistosoma haematobium, which are recognised by the terminal spine.

While heavy haematuria of either upper or lower tract origin will be accompanied by some proteinuria, persistent heavy proteinuria is virtually diagnostic of glomerular pathology. To eliminate postural and exercise effects, it is essential to measure proteinuria only in urine secreted by the kidneys during recumbency. This may take the form of a timed, overnight collection in which the proteinuria is expressed as mg/hour/m² body surface area, but is liable to error in small or enuretic children, and we found an excellent correlation with the protein:creatinine ratio measured in an early morning urine sample.37 The upper limit of normal, based on 377 healthy individuals aged 3–19 years, is 20 mg:mmol. The same early morning urine can be used to determine the calcium:creatinine ratio, which should be <0-7 mmol:mmol, and this should be done routinely in children with unexplained haematuria.

**IMAGING**

The former practice of performing intravenous urography on children with unexplained haematuria has been superseded by real time ultrasonography that is capable of detecting all gross lesions equally well and some, such as renal cysts or a non-functioning hydronephrotic kidney, more effectively. It should be combined with a plain abdominal radiograph, however, as a small, radio-opaque calculus in the ureter may escape detection. Children who show clearcut nephritic signs, as already outlined, and have proteinuria and granular casts in addition to haematuria, can be investigated as cases of presumed glomerulonephritis without the need for preliminary imaging. Cystoscopy and retrograde urography are rarely indicated in children with isolated haematuria, who are best referred to a nephrologist rather than a urologist.

**THE ROLE OF RENAL BIOPSY**

In practice most children presenting with haematuria prove to have negative initial screening procedures as outline above, and the findings point towards a glomerular origin. The final step in diagnosis is the further evaluation of glomerulonephritis, in which renal biopsy plays a major part. This is an invasive procedure, however, which should not be undertaken lightly. Some children can be adequately managed without biopsy, and the figure shows a scheme for assessing its need.

Patients who show heavy proteinuria in addition to haematuria are likely to have some kind of proliferative glomerulonephritis and should be investigated promptly. In poststreptococcal nephritis the serum antistreptolysin titre is not always raised, and it is essential also to measure the anti-DNase B titre. The serum C3 is usually depressed but returns to normal within eight weeks; therefore, if the initial concentration is reduced, the measurement must be repeated after four to eight weeks, for confirmation. A persistently low concentration, usually together with persisting, heavy proteinuria, would be strongly suggestive of mesangiocapillary glomerulonephritis,8,9 and renal biopsy would be indicated.

A decision is reached with somewhat greater difficulty in children whose proteinuria is minimal or absent, who in fact account for most patients presenting with haematuria. It cannot, unfortunately, be argued that the condition is necessarily benign, for the Alport nephropathy is rarely associated with heavy proteinuria before 10 years of age in boys, and much later in girls.17 On the other hand, as there is no effective treatment for either Alport's syndrome or IgA nephropathy, diagnosis is not a matter of urgency. My practice is to instruct the mother to test early morning urine samples for blood every two weeks for a period of six months, using Hemastix strips, and record the results. At the same time she is asked to test urine from all first degree relatives, avoiding the menstrual periods in adult women.

If tests on the child show more or less continuous microscopic haematuria, or if family testing is positive, renal biopsy should now be arranged. If, on the other hand, family testing is negative and the child's haematuria is intermittent, a decision may be reached to defer biopsy, and the parents can be reassured with reasonable confidence that a serious underlying disorder is unlikely. Unlike proteinuria and purely microscopic haematuria, visible haematuria is apt to cause the parents considerable anxiety, and in these circumstances biopsy may be warranted in order to increase the paediatrician's confidence in reassuring them.

Finally, to attain a high success rate combined with low risks, the performance of renal biopsy requires initial training and continuing experience, which are best obtained in a centre with a turnover of about 50 biopsies a year. In the past I have many
Haematuria confirmed microscopically
Non-glomerular causes excluded

Proteinuria
Persistent, heavy

Complement
Streptococcal antibodies

Renal function
Coagulation screen

RENAL BIOPSY

Serial urine tests,
child and 1st degree
relatives, 6 months

Haematuria
persists

Reassurance

Follow up

Intermittent haematuria
and family -ve

Family +ve
Continuous
haematuria

Accepted

Rejected

Figure A scheme for the selection of children with haematuria for renal biopsy.

sometimes had to repeat biopsies carried out by enthusiastic but inexperienced ‘handymen’, and it is my policy not to teach the technique to paediatric trainees unless they are committed to a career in paediatric nephrology. The same principles apply to the processing and histological interpretation of specimens. It should be borne in mind that IgA nephropathy requires immunofluorescence and the Alport nephropathy electron microscopy to establish the diagnosis; in the early stages they are indistinguishable by light microscopy alone. I would therefore regard it as unethical, today, for biopsy to be performed in any circumstances where the appropriate expertise and facilities do not exist. In the United Kingdom most (but still not all) biopsies are now performed by trained paediatric nephrologists working in hospitals affiliated to medical schools, and these are the appropriate points of referral for children with haematuria. Moreover, if we are to continue extending our knowledge of the natural history of these still poorly understood disorders, the collaboration of skilled adult nephrologists in the ongoing care of young adult patients is equally desirable.

This article is based on a lecture given to the Philippine Society of Nephrology on 25 March 1988, and is reproduced (modified) by courtesy of The Philippine Journal of Nephrology.

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*Arch Dis Child* 1989 64: 159-165
doi: 10.1136/adc.64.1.159