PYELONEPHRITIS IN CHILDREN

An Interim Review of Recent Literature

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PYELONEPHRITIS is now a fast-changing subject, with which the general reader may keep abreast only if frequent attempts are made to bring together published work from different sources. This survey aims to provide a balanced account of recent concepts, but is in no sense exhaustive.

Incidence of the Disease

Among childhood infections those of the urinary tract are second in frequency only to respiratory infections, and are the commonest bacterial infections under two years of age (Pryles, 1960; Deluca, Fisher and Swenson, 1963). The incidence of overt urinary infections in the general population is estimated at 8 per 1,000 per annum (Percival, Brumfitt and Louvois, 1964), and in American schoolgirls at 1.4% of the school population per annum (Kunin, Deutscher and Paquin, 1964). Between 1 and 4% of hospital admissions of children are for this disease (Stansfeld, 1954); 3 to 4% of recent admissions to an acute paediatric ward in London were for urinary infections (Burke, 1961). On the other hand, in the Newcastle survey of 1,000 families, only 3 out of 847 children were noted to have pyelonephritis in five years; all relapsed. The incidence of "significant bacteriuria", which is often symptomless, (for definition see below) is higher, especially in girls; 1% of schoolgirls in a recent large American survey were found to have this (Kunin, Southall and Paquin, 1962; Kunin and others, 1964). Forty per cent of young women with symptomless bacteriuria in early pregnancy later developed pyelitis of pregnancy (Kincaid-Smith, 1964; Percival, Brumfitt and Louvois, 1964). The highest incidence of bacteriuria was found in girls aged between 15 and 19 (Kunin, Deutscher and Paquin, 1964). Most clinicians find that the onset of infection is most frequent under one year old (Stansfeld, 1954; Smellie, Hodson, Edwards and Normand, 1964), though some assert that the peak incidence is among girls aged three to five (Deluca, Fisher and Swenson; Gross, Randolph and Wise, 1963).

But in infancy the diagnosis is often missed: in one autopsy series it had been missed clinically in 8.3% (Pryle and Neumann, 1962). The initial urinary infection often occurs in the newborn period; in one series 0.3% of hospital births (Smellie and others, 1964) and in another 1.5% (James, 1959) were considered to be infected. In fact, the incidence among the newborn may be higher than in other age groups; congenital defects in the kidney may predispose (Porter and Giles, 1956). Postmortem studies suggest that the prevalence of urinary infection is still underestimated (Kleeman, Hewitt and Gaze, 1960); about 2% of routine autopsies on American children disclose evidence of pyelonephritis (Pryles and Neumann, 1962; Spark, Travis, Dodge, Dalschmer and Hopps, 1962; Macaulay, 1964), but the difficulties in diagnosis of this infection from postmortem material must be borne in mind. An increased incidence of pyelonephritis in siblings has been noted (Kunin, Deutscher and Paquin, 1964).

The Course and Prognosis of Childhood Urinary Infections

A tendency for the infection to relapse or to become persistent is an alarming feature of pyelonephritis. Some 80-95% of treated primary infections are "cured" (when defined as free from bacteriuria six weeks after cessation of treatment), but about half of these have further periods of infection (Macaulay and Sutton, 1957; *Lancet*, 1963). Recurrences seem more common in older children than in infants (Burke, 1961) and especially so in girls of the six to ten age group (Williams and Sturdy, 1961). Persistence of infection is common, mainly in girls (Dunn, Hine and MacGregor, 1964; Woodruff and Everett, 1954), and one third to one half of continuing infections are asymptomatic (Steele, Leadbetter and Crawford, 1963; Dunn and others, 1964). Admittedly the significance of "significant bacteriuria" as the only finding is still debatable, but there seems to be little tendency for this to die out spontaneously (Kass, 1956; Kleeman and others,

1960; Spence, Murphy, McGovern, Herdion and Pryles, 1964). Persistent infection has been found with different frequency in different surveys, in 10% (Burke, 1961), in 25% (Dunn and others, 1964), in 39% (Woodruff and Everett, 1954). Of the chronic and recurrent groups the outcome varies, but the prognosis is believed to be worst when the onset is under two years of age. Some clear up, spontaneously (Kunin, Deutsches and Paquin, 1964) or with treatment (Turck, Browder, Lindmeyer, Brown, Anderson and Petersdorf, 1962; Macaulay, 1964) or at adolescence (Turner-Warwick, 1962; Williams, 1964). Others progress to renal failure (Rosenheim, 1963). The follow-up in adults after 20 years can be appalling. In a survey relating to the pre-antibiotic era, 43% of young women who had been treated for acute pyelonephritis had serious urological disease after 16 years (Hanley, 1964). There is not yet much information about the long-term prognosis for children. The incidence of toxæmia of pregnancy and pyelitis of pregnancy is known to be unusually high when there is a history of urinary infection in childhood (Steele and others, 1963), although a history of childhood infection was found in only five out of 75 pregnant women with pyelitis in one enquiry (Woodruff and Everett, 1954). There seems to be little correlation between the number of recurrences and the effect after some years on the kidneys (Steele and others, 1963). The equal sex incidence of chronic pyelonephritis at autopsy in adults does not seem consistent with the much higher incidence of symptomatic infections in girls, suggesting that the one is not the direct antecedent of the other (Macaulay, 1964). However, some girls with recurrent infections have been observed to develop progressive loss of kidney parenchyma with a fatal issue (Williams, 1965). Although pyelonephritis is the second commonest cause of hypertension in adults, in two-thirds of such cases no history of recurrent urinary infection could be obtained (Kincaid-Smith, McMichael and Murphy, 1958). Indeed, it is said that a history of acute pyelonephritis is rare in advanced chronic pyelonephritis (Kimmelstiel, Kim, Beres and Wellman, 1961). On the other hand, in a recent series of 200 children seen for urinary infection at a hospital, 13% had X-ray evidence of chronic pyelonephritis (Smellie and others, 1964).

Whatever its ultimate results, chronic urinary infection is difficult to eradicate. With chemotherapy the prognosis is still depressing (Macaulay and Sutton, 1957). Uncomplicated primary infections treated continuously for up to two

years still show a 7% relapse rate afterwards (Campanacci, Bonomini and Zuchelli, 1963). In chronic or recurrent infections in adults there is only a 10% (Lancet, 1963) or 20% (Turck and others, 1962) cure rate, in spite of really prolonged treatment (up to two years) (Williams, 1963). In children, after conventional treatment of acute infections there may be a 25% persistence rate (Dunn and others, 1964). There is not much evidence that prolonged drug treatment will produce better figures (Lancet, 1963), unless perhaps in infants (Stansfeld and Webb, 1954), though assertions are made to the contrary (Smallpeice, 1958). In adults, non-antibiotic urinary disinfectants such as methenamine mandelate (Holland and West, 1963) are capable of giving as good results as the powerful modern antibiotics tetracycline, chloramphenicol and kanamycin (Turck and others, 1962), especially in older age groups (Lindmeyer, Turck and Petersdorf, 1962). Because so many infections are clinically silent, prolonged follow-up of treated cases is essential (Lancet, 1963). Such follow-up studies in children are in progress in a number of centres and should soon provide facts about the true prognosis in childhood. Early treatment of primary infections is important (Deluca and others, 1963), for delay in diagnosis increases the relapse rate (Stansfeld and Webb, 1954). Once pyelonephritic scarring of a kidney has occurred, infection is very difficult to eradicate (British Medical Journal, 1964). Delay in diagnosis is common, and averaged 18 months in one recent survey (Deluca and others, 1963). In another (Spence and others, 1964), 47% of children sent to hospital had had symptoms for one year or more, and in a third series, only 30% of children had been sent to hospital with a suggestion of the correct diagnosis (Smellie and others, 1964).

Clinical Features

In infancy, anorexia, loss of weight, vomiting and failure to thrive are the main symptoms; in older children, fever or abdominal pain (Burke, 1961; Smellie and others, 1964). Only 25% have micturition symptoms (Burke, 1961). Hæmaturia occurs in 10% of acute attacks (Kleeman and others, 1960; Burke, 1961). Recurrent febrile urinary infections are known to occur in older girls (Williams and Sturdy, 1961), and the symptoms tend to be the same each time (Burke, 1961). In older children chronic infection may be quite silent, but close questioning will often uncover some disregarded urinary symptom, such as enuresis, frequency or

dysuria (Dunn and others, 1964). Ureteric reflux occasionally gives rise to pain in the loin on micturition (Forsythe and Wallace, 1958). Episodes of partial or complete urinary retention may be described (Gross and others, 1963). Important clues may be revealed if questions about the rate and force of the urine stream, and whether straining is present, are a part of the routine enquiry (*New England J. Med.*, 1963; Gross and others, 1963). However, analysis of symptoms does not allow a judgement to be made of which cases have urological abnormalities, and which have not. (Forsythe and Wallace, 1958; Kunin and others, 1964). Neither is the severity of symptoms proportional to the extent of existing, or of future, renal damage (Steele and others, 1963). The growth of patients with X-ray changes of pyelonephritis is sometimes a little reduced. There is occasionally hypertension, or another congenital malformation (Smellie and others, 1964). Polyuria and nocturia are early signs of serious renal impairment (Kleeman and others, 1960).

Diagnosis of Urinary Infection

The danger of catheterisation as a means of introducing infection is increasingly recognized, especially in obstetric practice (Brumfitt, Davies and Rosser, 1961). The risk of infection in children is probably less (though it was 7% in one series (Vertanen, Oksanen and Pettonen, 1962); catheterisation should not be withheld if needed for urgent diagnosis, retention, non-cooperation or uncertainty (Pryles, 1960). But in children the bacteriological correlation between catheter and clean-voided specimens can be 96% (Pryles, 1960) and at all ages mid-stream specimens without bacterial contamination can be obtained from a high proportion of both sexes (Clarke, 1960; Pryles, 1960; Vertanen and others, 1962; Cattell and Lefford, 1963). The most precise results are obtained from suprapubic aspiration of the bladder (Monzon, Ory, Dobson, Carter and Yow, 1958); this method gives only a 93% bacterial correlation with catheter urine, but is higher if the first few millilitres of catheter urine are discarded (Pryles, 1960). Many different techniques of perineal cleansing are employed before taking clean specimens (Brumfitt and others, 1961; Cattell and Lefford, 1963; Houston, 1964); benzylkonium chloride 1 in 1000 is much used (Little, 1962), polybactrin spray has advocates (McLeod, Mason and Pilley, 1963), but soap-and-water seems satisfactory (Clarke, 1960). Different methods of cleansing do not seem to influence urine cell counts (Lincoln and Win-

berg, 1964). The plastic bags, much used for obtaining specimens from young children, are liable to introduce contamination into bacterial counts, but have less influence on cell counts (Houston, 1964).

Proteinuria is of little aid in detecting urinary infection (Burke, 1961; *Lancet*, 1962a and b; Steele and others, 1963; Dunn and others, 1964; Smellie and others, 1964); albumin was found as frequently in the urines of unaffected school-girls, as in those with significant bacteriuria (Kunin and others, 1964). The lack of a simple but reliable screening test for infection is still lamented (*Lancet*, 1962). Controversy has focussed upon the relative accuracy of methods which estimate bacteria, and of those which count cells, in the urine. The correlations between urinary cell concentration, timed cell excretion rates, and bacterial colony counts are not close, and misleading results can come from relying upon any one of them (Osborn and Smith, 1963). In America colony counts are preferred (Brumfitt and Percival, 1964; Spence and others, 1964). For children in hospital pus cell counts have been found as useful as bacterial counts in identifying infections; with either method there were 13-25% doubtful results; when the methods were used in conjunction uncertainty was reduced to 6% (Houston, 1964).

Direct examination of freshly voided urine may show organisms under the microscope; bacteriuria of this magnitude is never due to contamination, so this is a valuable screening technique (Gardborg, 1959; Dunn and others, 1964). Again, if the uncentrifuged sediment of a urine shows organisms after Gram staining, the bacterial count is nearly always above 100,000/ml. (Pryles, 1960; Kunin and others, 1964). Laboratory techniques for demonstrating bacteriuria employ quantitative, semiquantitative, or chemical screening methods. Urine is an excellent culture medium, so within two hours at room temperature a large increase in bacterial numbers may occur (Pryles, 1960). This can be prevented by refrigeration of fresh specimens at 4°C, which preserves the bacterial content unaltered for 2-7 days (Pryles, 1960; Houston, 1964). Bacterial colony counts on large numbers of fresh urines show a bimodal distribution, with peaks at less than 10,000 and at more than 100,000 organisms/ml. There is much evidence that organisms derived from the urethra or vulva never exceed 10^4 per ml., whereas bacteria rapidly multiply in the bladder to reach numbers in excess of 10^5 per ml., the level of "significant bacteriuria" (Kass,

1956, 1960). Significant levels may have to be slightly higher in the case of young children (Houston, 1964). Quantitative bacterial counts on urine are made by the surface viable, or pour plate techniques (Brumfitt and Percival, 1964). These methods are too time-consuming for most routine laboratories, so semi-quantitative modifications are often used. Using fresh uncentrifuged urine and a standard loop, colony counts of more than 200 equate with more than 10^5 organisms per ml., and counts of less than 90 with less than 10^4 organism per ml. This is sufficiently accurate for clinical practice (O'Sullivan, Fitzgerald, Meynell and Malins, 1960). Another technique employs a blotting paper strip dipped into urine and pressed on to the culture medium; results have been standardised against pour plate counts (Leigh and Williams, 1964). Conventional methods of descriptive reporting on the bacteriology of urine have been compared with the results of bacterial counting; it is claimed that if standards are rigorous, closely similar conclusions will be drawn from each method, and that experimental results are not necessarily invalidated by failure to carry out bacterial counts (Clark, 1960; Guttman and Stokes, 1963). The T.T.C. test is a chemical screening method based upon naked-eye observation of colour change in the urine after incubation of urine with test material in a water bath (Simmons and Williams, 1962). It is claimed to give a positive reading with bacterial counts of gram negative organisms over 100,000/ml., and has proved successful in detecting 86% of antenatal women with asymptomatic bacteriuria of pregnancy (Kincaid-Smith, Bullen, Mills, Fussell, Huston, and Goon, 1964), and even better results are reported. The level of certain enzymes is also reported to be raised in infected urines (Brenner and Gilbert, 1963).

Pyuria may result from other causes than urinary infection, from vaginitis, trauma, dehydration and nephritis, as well as at the end of a urinary infection when organisms have gone (Pryles, 1960). Until recently the criteria accepted by many authors as "significant pyuria" were not uniform (*Lancet*, 1962). A commonly employed criterion has been "more than five cells per high power field" (representing, if centrifuged, approximately 25 cells/cu. mm., if uncentrifuged, approximately 250 cells/cu. mm. (Stansfeld, 1962, 1963). On this basis, only 35% of children with significant bacteriuria had also significant pyuria (Kunin and others, 1962), and, in another series, only half the infected children had pyuria (Steele

and others, 1963). But this standard is no more acceptable than are the still much employed descriptive reports ("moderate numbers" or "scanty pus cells") which for CSF, with a similar range of cell numbers, are never countenanced (Stansfeld, 1962; Little, 1964). Of course, chronic pyelonephritis with a cell-free urine is well recognized (Clarke, 1960; Deluca and others, 1963; Leather, Wills and Gault, 1963), and both pyuria and bacteriuria may be intermittent (Stansfeld, 1954; Dunn and others, 1964); but bacilluria without pyuria, using a sensitive criterion, occurred only three times in 250 specimens from children (Stansfeld, 1962). Timed white-cell excretion rates, which do not seem to be much influenced by the rate of urine flow, are available for adults, but not yet for children (Houston, 1964). An upper limit of excretion of 400,000 cells per hour is not exceeded in normal men or women (Kass, 1956; Little, 1962; Gadeholt, 1964); this is probably the best measurement of pyuria (Gadeholt, 1964). Centrifugation in any cell counting technique introduces important errors, as it leads to considerable and unpredictable loss of cells (Gadeholt, 1964; Little, 1964). Cell counts in uncentrifuged specimens have been found in adults to give a good correlation with timed cell excretion rates; more than 10 cells/cu. mm. means more than 400,000 excreted per hour, while less than three cells per cu. mm. means less than 400,000 per hour with fair certainty; there is no sex difference (Little, 1964). Quantitative methods of leucocyte counting in a counting chamber are increasingly used for children (Stansfeld, 1954), and have less variation than methods based on high power field counts. It is however important to ensure a urinary pH of between six and eight (Stansfeld, 1962).

Semiquantitative wet film screening techniques of cell counting have proved useful in some hands (Dunn and others, 1964), though criticized by others in respect of variability (McGrackie and Kennedy, 1963). After infancy, 92% of urines from normal children contain less than 10 leucocytes/cu. mm. (Stansfeld, 1962). Older girls give more misleading cell counts (Houston, 1964). One centre accepts less than 10/cu. mm. as normal, more than 100 as infected, and intermediate values as dubious (Houston, 1964). A level of 50/cu. mm. or more is regarded by others as indicating infection (Stansfeld, 1954). In the newborn, counts greater than 25/cu. mm. in boys, or 50/cu. mm. in girls, are abnormal (James, 1959; Lincoln and Winberg, 1964). Neonates, especially males, may excrete epithe-

lial cells in considerable number and cause confusion (Lincoln and Winberg, 1964); differential staining may then make counting easier (Sternheimer and Malbin, 1957; Prescott and Brodie, 1964; Houston, 1964). Taking a level of 10 leucocytes/cu. mm. as "significant pyuria", some 14% of admissions to a children's hospital were found to have it, though counts below 50/cu. mm. seldom turned out to be abnormal (Stansfeld, 1954, 1962). In general, those who have studied the subject over a long period now accept that the diagnostic value of leucocyte counts is comparable to that of bacterial counts (Osborn and Smith, 1963). When chronic pyelonephritis is suspected, attempts to stimulate leucocyte excretion can be made, using intravenous bacterial pyrogen (Leather and others, 1963), or, probably with more reliability (Montgomerie and North, 1963), with oral steroid drugs (Huth, Chalmers, Macdonald and de Wardener, 1961; Little and de Wardener, 1962). There are no reports of the use of these methods for children. There is need for a test to distinguish reliably between infection involving the kidney, and that confined to the lower urinary tract (Brumfitt and Percival, 1964). The presence of leucocyte casts in urine means renal infection, and by using a special stain, morphological differences are apparent between leucocytes of renal origin and those from more distal sources (Sternheimer and Malbin, 1957; Poirier and Jackson, 1957), which can be used as a diagnostic aid. When the serum from a patient with an acute urinary infection is used for direct agglutination against organisms obtained from the urine, a high and rising titre seems to correlate with involvement of renal tissue. A titre of more than 1:160 suggests such infection: it falls rapidly when infection is controlled (Percival and others, 1964). However, in another large group of bacteriuric girls no such relationship was found (Kunin and others, 1964).

Reasons for Persistence of Infection

The insidious advance towards chronic pyelonephritis, which is so resistant to treatment, has prompted much speculation about predisposing factors. Major structural abnormalities of the renal tract are readily demonstrated, and do not contribute to the problem under discussion. The megacystis-megaureter syndrome, for example, is found in 6.5% of persistent urinary infections (Kunin and others, 1964). A retrospective survey of a group of girls with recurrent urinary infections, previously investigated, failed to demonstrate any

child in whom serious obstruction had been overlooked (Williams and Sturdy, 1961). But about 10% of affected girls show recurrence or persistence of infection, and a large proportion (variously estimated at 25% (Dunn and others, 1964), 50% (Spence and others, 1964) or 75% (Macaulay, 1964) have structurally normal urinary tracts. It is plain that damage from one attack confers in some way a susceptibility to further attacks (*Lancet*, 1963), and in experimental pyelonephritis intra-renal scarring permits of infection more readily, as also do areas of renal dysplasia (Kleeman and others, 1960). Non-bacterial agencies, such as an underlying virus infection, or auto-immune reactions, or progressive renal vascular damage have been considered, without good evidence to favour them (Brumfitt and Percival, 1964). Bacteria are in fact probably responsible; it has been suggested that they could persist within the kidney as spheroplasts or protoplasts (Brumfitt, Percival and Williams, 1964), but the tendency for one organism to be replaced by another after treatment argues to the contrary (Gardborg, 1959; Turck and others, 1962). There may be "pyelopathic" strains of *E. Coli* (Brumfitt and Percival, 1964; Sweet and Wolinsky, 1964). Again, anti-bacterial substances are known to exist in normal urine, and may be reduced in diseased states (Kleeman and others, 1960). But of late years increasing attention is being given to vesico-ureter reflux as a factor promoting persistence of infection.

Vesico-ureteric Reflux

Retrograde movement of urine from the bladder up the ureters rarely if ever occurs in normal children (Hodson and Edwards, 1960; Williams, 1964; Spence and others, 1964), although it is a normal finding in rats, and can be borne in dogs under experimental conditions for long periods without ill-effects except some progressive depression in ureteric peristalsis (Scott, 1962). Reflux occurs in man in congenital megaureter, in bladder wall abnormalities, with neurogenic lesions, with lower urinary obstruction, and with chronic pyelonephritis (Turner-Warwick, 1962; Gross and others, 1963; *New England J. Med.*, 1963). It is also observed frequently in association with trigonitis and urethritis in young women as a transient phenomenon, and in this way probably disposes to ascending infection of the kidneys (Hanley, 1964). Its occurrence in obstructive uropathy is generally accounted for by the protrusion of a mucosal sacculi at the ureteric orifice, while in non-obstructive urinary infections reflux is

ascribed either to a congenital deficiency of ureteric muscle, to a shortened intramural course from a contracted bladder, or to rigidity from oedema of the bladder wall (Williams, 1964). In different patients, reflux may occur at different levels of intra-vesical pressure, and of bladder filling (Melick, Brodeur and Karellos, 1962b). Ureteral competence is achieved by a longitudinal crumpling of intra-vesical mucosa (a "whistle-valve" effect), and if this fails reflux may occur without any rise of intravesical pressure (Melick, 1962a; Stephens and Lenaghan, 1962). Reflux may remain unilateral, as free reflux quickly reduces pressure within the bladder. It may disappear spontaneously (Turner-Warwick, 1962), and because it is not present at one examination, it is no proof that it was never present (Johnston, 1963); it is occasionally seen with a sterile urine and no evidence of previous infection. It may occur for the first time during a urinary infection (Hodson and Edwards, 1960), and is recorded in 18% of all infections in girls (Kunin and others, 1964). In recurrent urinary infections reflux is commoner in children than in adults, and is reported in 15-30% of non-obstructive pyelonephritis (Palken and Kennelly, 1960; Deluca and others, 1963). Radiographic evidence of chronic pyelonephritis without reflux at any time has seldom been found (Williams, 1965), and the triad of chronic pyuria, vesico-ureteric reflux and pyelonephritic scarring of the kidney is a familiar one (Johnston, 1963). Reflux has been reported in 70-80% of children with chronic pyelonephritis (Allen and Burrows, 1964; Hodson, 1964). There is frequent association with hydronephrosis, with renal scarring and with duplex kidneys (Smellie and others, 1964). There is good evidence that the effects of reflux back pressure on the kidneys may be serious (*New England J. Med.*, 1963), and that pyelographic abnormalities may be caused, presumably via effects upon the calyceal blood vessels (Williams, 1964). These effects are calyceal blunting, general diminution in size of the kidney, and failure of the kidney to grow (Hodson, 1959; Hodson and Edwards, 1960; Hodson, Drewe, Karn and King, 1962). In most cases a combination of backpressure and infection is present, but the only certain radiographic indication of infection (whose other effects are indistinguishable from those of reflux) is coarse localised scarring of the renal substance (Hodson, 1959), which takes two to seven years to develop (Hodson, 1964). Reflux is present so often when there is X-ray evidence of renal damage in pyelonephritis, that it may

be a necessary condition for damage to occur (Allen and Burrows, 1964). The ill-effect of reflux is well demonstrated in patients with congenital double ureter, the upper calyx of whose kidneys is always drained by a ureter opening low in the bladder, after an intramural course of exceptional length. The other ureter has a short intramural course, and therefore is apt to become incompetent, so allowing reflux to occur. In these patients it is always the lower calyces which become damaged and infected (Williams, 1962). In adults, where reflux and chronic infection are associated, the untreated prognosis before renal failure is two or three decades at most (Hodson and Edwards, 1960). If there is an element of obstruction, the renal failure may be of a kind with a normal blood urea level, but with excessive water and electrolyte losses (*Lancet*, 1962; Jones and Mills, 1964). There may be renal osteodystrophy (Hodson and Edwards, 1964).

Lower Urinary Obstruction

There is no general agreement upon how often persistent infection is associated with minor degrees of obstruction to the lower urinary tract, though this is a well-recognized association with ureteric reflux (Hodson, 1959; Hodson and Edwards, 1960; Williams and Sturdy, 1961; Turner-Warwick, 1962; Deluca and others, 1963; *New England J. Med.*, 1963; Gross and others, 1963). In a long follow-up averaging sixteen years it was found that all children with advancing renal disease had obstruction to urinary outflow (Steele and others, 1963). Organic abnormalities of the urinary tract, including reflux, are found in 50-75% of children with persistent infections (Allen and Burrows, 1964; Dunn and others, 1964). Obstructive uropathy has been reported in 16% (Deluca and others, 1963) and in 35% (Steele and others, 1963) of large surveys of such children. Obstruction is most often at the bladder neck in girls, and the lack of clear-cut objective criteria for this diagnosis, has made the entity an unsatisfactory one. Bladder neck obstruction cannot be diagnosed endoscopically, and diagnosis depends upon the observation of non-progressive bladder muscle hypertrophy, with overgrowth of tissue at the bladder outlet, in the absence of more distal obstruction (Williams and Sturdy, 1961). In practical terms this means the presence of residual urine (not due to nervousness or to reflux), and, on cystoscopy, the presence of trabeculation of the bladder wall. Suggestive additional features are raised intravesical voiding pressure, ureteric reflux and

sacculation of the bladder (Williams and Sturdy, 1961; Gross and others, 1963). Except for bladder neck hypertrophy itself, all these features can be due to other causes, and even now bladder neck obstruction is not accepted by all surgeons (Johnston, 1963), but most consider it real and important (Williams and Sturdy, 1961; Gross and others, 1963; Williams, 1965), with an onset usually under three years old, and present, according to one estimate (Spence and others, 1964), in 25% of recurrent infections, though this may be too high a figure (Williams, 1965). The "spinning-top appearance" of the urethra during a voiding cystogram, previously thought to indicate bladder neck obstruction, is probably a normal appearance. Likewise the "wide bladder neck deformity" in girls, regarded as an abnormality predisposing to infection by some workers (Forsythe and Wallace, 1958), may be a normal variant (Burrows and Allen, 1964).

Surgical Treatment of Ureteric Reflux and Bladder Neck Obstruction

About ureteric reflux there is not yet sufficient evidence to justify invariable corrective surgery (Scott, 1962; Turner-Warwick, 1962; Macaulay, 1964), nor has time enough elapsed to assess fully the results of corrective procedures (Johnston, 1963). Most surgeons advocate first a period of conservative management, with antibiotics and the use of "triple micturition" (Gross and others, 1963). For bladder neck obstruction, graduated urethral dilatations are urged by some surgeons (Palken and Kennelly, 1960; Knappenberger, 1963). The presence of dilatation of the upper urinary tract is a widely accepted indication for operation (Turner-Warwick, 1962; Gross and others, 1963), most often a reimplantation of the ureters into the bladder wall, as well as a plastic procedure upon the bladder neck. Postoperative follow-up for several years in one series showed that infection was unlikely to return if there had been no pre-operative dilatation of the upper urinary tract (Gross and others, 1963). Another experienced view is that successful reimplantation of the ureters will lead in most instances to control of infection without chemotherapy (Williams, 1964), and that results justify bladder neck surgery alone in a relatively small number of girls. Unless reflux coexists, pyelonephritis is not usual with bladder neck obstruction (Williams, 1965).

Techniques of Investigation

Excretion pyelography. This will display

dilatation of the calyceal system in about 13% of persisting childhood urinary infections (Kunin and others, 1964). Blunting or shortening of the calyces, the size of the kidneys, and the presence of coarse localised depressions upon them, may also be revealed. For small children tomography (one or two cuts) may help to evaluate the pyelogram. Concentration of dye may be remarkably good even with severely damaged kidneys (Hodson, 1959). Weakening of the picture in later films may indicate dilution from ureteric reflux (Hodson, 1964). Tonelessness of the lower ureters (a "flabby dilatation"), or a ureter visible in its entire length may be pyelographic pointers to the presence of reflux (Marshall, 1962; Turner-Warwick, 1962; Johnston, 1963). Kinking may be visible at the upper end of such a ureter (Williams, 1964). The "ureteric spurt reaction", a jet of urine from the ureteric orifice across the bladder, may be noted in the I.V.P. of children with urinary infections (Nevin, Cline, and Haug, 1952). A nephrogram may be obtained by the rapid intravenous injection of 50 ml. of 70% organic iodine solution (Hodson, 1959). A pyelogram is advocated in all first attacks of urinary infections, as soon as the infection is controlled (*British Medical Journal*, 1964; Spence and others, 1964).

Cysto-urethrography. A voiding or micturating cystogram is necessary for the diagnosis of ureteric reflux. If X-ray screening is possible during the procedure, more useful results will be obtained (Allen and Burrows, 1964). The procedure is indicated in recurrent infections, or if reflux is suspected on the pyelogram, or if renal scarring is visible (*British Medical Journal*, 1964). The procedure is often more useful than a pyelogram as a first investigation in neonates (Smellie and others, 1964). Reflux may be difficult to demonstrate. The earliest indication may be fleeting filling of the lower ureter (best seen in an oblique-view) during micturition. More obvious reflux produces distension of the pelvis of the kidney during voiding (Johnston, 1963). At all ages, a cystogram is more often revealing in urinary infections than a pyelogram. Thus, in one series of 500 children submitted to both procedures, the cystogram was abnormal on 237 occasions and the pyelogram on only 27 (Allen and Burrows, 1964). Another large series reported an abnormal IVP in 22% and an abnormal cystogram in 44% of cases (*Lancet*, 1962). Using the two procedures together, the need for retrograde pyelography is virtually eliminated (Forsythe and Wallace, 1958).

Hodson, 1959; Burrows and Allen, 1964).

Cineradiography. This is a refinement of the voiding cystogram, but provides little information that cannot be obtained by other techniques (Clarke, 1960; *New England J. Med.*, 1963; Smellie and others, 1964).

Cystoscopy. An essential investigation in the diagnosis of bladder neck obstruction.

Estimation of residual urine. Aid may be obtained by introducing floating lipiodol into the bladder at the time of the cystogram. If there is no residue, all should be excreted within 24 hours. With reflux, radio opaque material may ascend to the pelvis of the kidney (*New England J. Med.*, 1963).

Estimation of voiding pressures within the bladder. This is useful for assessing the results of operation; measurement can be made through a small urethral polythene tube (*New England J. Med.*, 1963; Gross and others, 1963). Normal intravesical pressures are 0-18 mm. Hg. resting, rising to 70-100 mm. Hg. voiding (Melick, 1962a). Other authors record lower voiding pressures of 15 to 20 mm. Hg., and regarded pressures of 40-50 mm. Hg. or more as indicative of obstruction (Gross and others, 1963; Spence and others, 1963). Reflux may reduce this.

Detection of reflux by a radioactive isotope. By using intravenous ^{131}I -hippuran, a nephrogram can be obtained with a scintillation counter during the passage of the dye through the kidney, and again during micturition if there is reflux (Dodge, 1963).

Aortogram. This investigation is of special value if hypertension is present, or in other cases where chronic disease may be unilateral. In one centre an aortogram is regarded as the next step if excretion pyelography and a voiding cystogram prove insufficient (Hodson, 1959).

Renal biopsy. The results of this are generally disappointing in pyelonephritis (see below).

It is generally agreed that incomplete study of these cases, which may lead to premature or misplaced surgery, is dangerous (*New England J. Med.*, 1963).

Bacteriology

A pure growth of organisms is obtained from the urine in some three quarters of childhood urinary infections. Of these *E. Coli* accounts for the majority, 60-80%. *B. Proteus*, often in mixed growth, is found in 12-17%, cocci (*Staph. aureus* and enterococci) in 6-8%, and *pseudomonas* in 4% (Gardborg, 1959; Pryles, 1960; Deluca and others, 1963; Kunin

and others, 1964). *Pseudomonas* and *proteus* are both related to instrumentation or to surgery (Kleeman and others, 1960), or to previous drug treatment (Turck and others, 1963). *Staphylococcus aureus* has been recorded as the second commonest organism in pure growth (Pryles, 1960). In recurrences, a new strain of organism is commonly found; estimates for this even vary from 30-87% (Kunin and others, 1964; Spence and others, 1964). Treatment frequently leads to replacement by a different organism in the urine (Gardborg, 1959; Turck and others, 1962). Renal biopsy, presumably because of the patchy nature of the inflammatory process, has not yielded useful bacteriological information; results have been described as "mystifying and sparse" (Kleeman and others, 1960).

Pathology

The route of infection of the urinary tract in most cases is regarded as ascending. Haematogenous infection which certainly occurs in staphylococcal cases, must be accepted as a rare possibility (Kleeman and others, 1960). Experimentally, haematogenous infection by gram-negative organisms will only occur in abnormal renal conditions, such as ureteric ligature, are present (Brumfitt and Percival, 1964). Organisms can ascend a stagnant film of fluid, and they can be found, according to one paper, at 5 cms. depth in the male urethra (Spence and others, 1964), so ascent to the bladder would not be difficult. Urethritis is common in many adult women (Brumfitt and Percival, 1964), and cystourethritis precedes acute pyelonephritis in many young women; transient reflux up the ureter has been observed many times in the former condition (Hanley, 1964). The concept in some cases of lower urinary infection without pyelonephritis is gaining ground (Mackinnon, 1964). To allow of multiplication of organisms within the bladder a disturbance of dynamics is usually necessary, especially deficient emptying (Brumfitt and Percival, 1964; Spence and others, 1964).

When inflammation of the renal pelvis is present, renal parenchymal infection is almost invariable (Weiss and Parker, 1939). Acute pyelonephritis is primarily an inflammation of the interstitial tissues of the kidney. Starting in the medulla, the septic process soon bursts into the tubule, and leucocytes and organisms are released into the urine. Glomeruli are remarkably resistant to the suppurative process, although they too become involved in an "invasive glomerulitis". Haematogenous

staphylococcal pyelonephritis, the so-called carbuncle of the kidney, gives rise to constitutional symptoms with local tenderness, but often at first no pyuria. Such infections usually heal completely.

Features by which to differentiate kidneys damaged by healed or chronic pyelonephritis from other renal disturbances have been much discussed, and absolute criteria are hard to find (Weiss and Parker, 1939; Kimmelstiel and others, 1961). In general, such kidneys are irregularly contracted, often nodular, with adherent thickened capsules and flat U-shaped scars. The pelvis may be thickened and infiltrated. Renal papillae are atrophic, and calyces dilated and shortened. Within, there is a characteristic patchiness of involvement, with hyperplasia of unaffected nephrons. The interstitial tissues are much infiltrated with lymphocytes and plasma cells but the presence of many polymorphs is essential to the inflammatory diagnosis. Many tubules show dilatation and atrophy and contain colloid material, so-called "thyroid-like" areas, which are typical of pyelonephritis. The glomeruli are relatively well preserved, even in scarred areas; periglomerular fibrosis is common, and when advanced renal failure existed, focal necrosis of the kind described as "alterative glomerulitis" is frequently seen. Hyperplastic arteriosclerosis, ("onion-peel arteritis") of varying severity is regularly seen, and in many such kidneys there is an intermediate or "barrier" zone of relative preservation between an overlying necrotic and scarred cortex, and the contracted medulla with dilated calyces. Most of these changes are non-specific and the presence of abundant polymorphs and of thyroid-like areas are probably the most reliable registers of pyelonephritis. "Chronic active pyelonephritis" is a useful concept to denote the scarred pyelonephritic kidney in which some acute inflammatory change is still evident. A less common group of chronic pyelonephritic kidneys are smaller and evenly and diffusely contracted (Kincaid-Smith and others, 1958). They may show adenoma-like nodularity (Weiss and Parker, 1939). These are seen in younger people, often with growth failure and renal rickets. They probably represent inflammation that has begun in very early life. ("Congenital hypoplastic kidneys," which are bilaterally small but of normal structure, are rarely if ever seen (Weiss and Parker, 1939)). In neonatal pyelonephritis, histological appearances may be confusing because of the presence of glomerular

crescents which suggest nephritis. Dysplastic lesions of the nephron may contribute to the incidence at this age (Porter and Giles, 1956).

There is no other type of nephropathy in which fluctuation in renal function occurs so frequently; patients may approach and recede from renal failure in a most variable manner, according to the state of activity of the inflammatory process. The residual renal units, though reduced in number, function normally; the consequence is decreasing regulatory flexibility with increasing azotaemia. Hyperchloraemic acidosis, or the salt-wasting syndrome, are rare biochemical accompaniments of chronic pyelonephritis.

Treatment

In the treatment of primary uncomplicated infections immediate good results can be obtained from most drugs, if the organism is sensitive (Pryles, 1964), but there is a 10-20% failure rate no matter what chemotherapeutic is used. Reliable data for judging the claims of one therapeutic regime over another are still scant. The need to obtain adequate renal tissue levels of drugs, as well as urinary levels, is being emphasised lately (Brumfitt, 1964), though the value of this has been questioned in the face of considerable successes with mandelamine and furadantin which do not achieve tissue levels at all (Kleeman and others, 1960). But for many gram negative organisms, the levels of antibiotic reached in the serum by conventional therapeutic dosage barely exceed, and seldom fully overreach, the minimum inhibitory concentration range (Brumfitt, 1964). The correlation between clinical effects of a drug in urinary infections and the results of *in vitro* bacterial sensitivity tests is not close; clinicians do not always pay regard to them (Pryles, 1964; Spence and others, 1964). The disc method is unreliable; the tube dilution technique is better, except for sulphonamides for whom "the patient himself is the best sensitivity test." (Pryles, 1964). Attention must be paid to pH adjustment of the urine in order to get the best results from drugs (Brumfitt and Percival, 1962). This is especially important for streptomycin which needs an alkaline urine, and for tetracycline which is more effective with an acid urine. The naturally occurring antibacterial substances in urine are thought to be more active at a low pH (Kleeman and others, 1960). Minimum and optimum lengths of treatment for acute infections have not been decided upon. In a small group of infants better results were obtained from a 6 months

than a 2 weeks course of drugs (Stansfeld and Webb, 1954), but when acute pyelitis was treated for 14 days in each month for a total of two years, there was still a 7% recurrence rate afterwards (Campanacci and others, 1963). In a controlled study of children with acute pyelonephritis, a relapse rate of 60% was found after 2 weeks treatment, 40% after 4 weeks, and 25% after 6 weeks (Spence and others, 1964). In persistent infection there is proved effectiveness in reducing recurrences from giving continued treatment for 6 months, in preference to short courses lasting 3 to 30 days (Deluca and others, 1963). If treatment in persistent cases is going to work, the urine is always sterile after 6 weeks. (Turck and others, 1962). A sulphonamide drug is still the most widely used for first attacks, and furadantin for chronic uncontrolled infections. Ampicillin is receiving much study and is the first choice for *Proteus* and *Enterococci* (Naumann, 1964); many strains of *E. Coli* show *in vitro* resistance to therapeutic levels of this drug, unless it is given parenterally (Brumfitt, 1964).

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