Current Practice

URINARY TRACT DISEASES

Infections of the Urinary Tract I—Diagnosis

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Symptoms suggesting infection of the urinary tract are common. In domiciliary practice they are encountered in 12 to 20 of every 1,000 consultations. During the past fifteen years quantitative bacteriology has shown the important role of bacteriuria in causing these symptoms. At a time when considerable medical resources are being invested in treating terminal renal failure, interest in a preventable cause of progressive renal disease is appropriate.

The article this week considers some of the present problems of the diagnosis of infections of the urinary tract; the inadequacies of a purely symptomatic approach; the significance of recent developments in bacteriological techniques; and the enigma of the pathology of pyelonephritis. A second article, appearing next week, will be devoted to the management of patients with infections of the urinary tract.

Symptomatic Infections

When a patient complains of frequency, painful micturition, and foul-smelling urine a diagnosis of "cystitis" is usually made. Nevertheless, recent studies in domiciliary practice in England, New Zealand, and Denmark indicate that these symptoms must be interpreted with more reserve, for only about half of those patients who complained of symptoms suggesting urinary tract infection were found to have infected urine. Patients who have the syndrome of dysuria, frequency, and urgency in the absence of an infected urine are said to have the "urethral syndrome." This syndrome may have a variety of causes. It is sometimes associated with chronic infection of the prostate in men and of the paraurethral glands in women. A history of precipitating factors such as cold weather, sexual activity, contraceptive devices, and sensitivity to deodorants and bubble baths is occasionally obtained. It is not always easy to relieve these symptoms.

When lower urinary tract symptoms are combined with fever, and tenderness in the loin is found on examination, it is usual to assume that the renal parenchyma has become infected, and acute pyelonephritis is then diagnosed. This concept is supported by finding a positive blood culture in some cases and raised antibody titres against the O antigen of *Escherichia coli* in many patients infected with this organism. Nevertheless, it is not only in those patients who develop loin pain and rigors that evidence of renal infection may be found.

Infections of the upper urinary tract may be present without causing any symptoms. This possibility was first disclosed by the surprisingly high incidence of chronic pyelonephritis found at necropsy, which had been undiagnosed during life. Though the histological criteria of some of the earlier necropsy studies are now questioned, these studies did serve to highlight the problem. Subsequent population surveys have shown that significant bacteriuria occurs frequently in the absence of symptoms, while further inves-

tigation of patients with asymptomatic bacteriuria has disclosed that many have evidence of renal involvement. In paediatric practice it is particularly important to be aware of the occult nature of urinary infections, and pyelonephritis must be excluded in any investigation of a child with persistent unexplained ill-health.

Symptoms of infection in the urinary tract must therefore be interpreted with caution. Their presence may give rise to false alarm; their absence to false complacency.

Quantitative Bacteriology

The work of Kass has established quantitative bacteriology as the indispensable laboratory aid for diagnosis, confirmation of cure, and follow-up of urinary tract infections. When the risks of bladder catheterization became known and precluded its continued use in diagnosis, quantitation of urinary cultures became necessary to exclude those cases in which the urine sample had become contaminated during its collection. Infection of bladder urine has been repeatedly shown to result in colony counts of over 100,000 per ml. of urine in the midstream sample. Contaminant bacteria usually produce counts of fewer than 10,000 per ml. Significant infection of bladder urine may be diagnosed with 80% confidence on a single sample; if two samples are positive, the confidence rises to 95%; if three, to 99%. False-positive results are likely if collection is faulty or there is delay in transmitting the sample to the laboratory or in processing the sample after its arrival. The result of the test is not appreciably affected by an hour's storage at room temperature or by up to 48 hours in a refrigerator. Persistently low counts may be encountered after the administration of an antibiotic. False negative results can be excluded only by suprapubic aspiration of urine from the bladder—a technique of collection which may also be valuable in children, in whom it may be difficult to obtain a midstream sample.

The stringent requirements for rapid transmission of samples have limited the application of quantitative bacteriology in domiciliary practice, where most of these infections occur and are treated. The introduction of the dip-inoculum technique, however, meets the needs of the busy general practitioner. The inoculum is presented on a plastic spoon or plate or glass slide (see Figure); it is dipped into the sample of "clean" freshly passed midstream urine, and then replaced in its sterile container and posted to the laboratory. A colony count can be made after overnight incubation in the laboratory. When significant bacteriuria is found subculture is often necessary to complete identification and always when sensitivity tests are required. This technique is simple and rapid, both for the clinician and the laboratory, and is in routine use in several clinics at St. Thomas's.

Pyuria reflects inflammation in the urinary tract. Urine should not be centrifuged to count the white cells, for this gives an unreliable estimation of the white cell excretion rate,

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Dip inocula. Left: Inoculum on microscope slide prepared in hospital microbiology department. Centre: Dip slide made by Oxoid Ltd., London S.E.1. Right: Dip spoon made by Medical Wire and Equipment Co. (Bath) Ltd., Corsham, Wiltshire.

particularly when there are small numbers of white cells (1 to 5) per high-powered field. A short cut to the white cell excretion rate is to count the number of cells per cu. mm. of uncentrifuged urine. If there are over 10 per cu. mm. the excretion rate exceeds 400,000 per hour, which may be taken to be the upper limit of normal. The white cell excretion rate is lowered in dehydration and raised in diuresis. It is also usually raised in urines containing over 100,000 bacteria per ml., but it is not a good screening test for bacteriuria since similar findings are present in various urinary tract diseases, notably in analgesic abuse and in tuberculosis of the renal tract.

Asymptomatic Bacteriuria

Bacteriuria is a laboratory diagnosis not a disease. If symptoms and signs of infection are present the isolation and identification of the infecting organism provide a precise criterion for diagnosis and specific treatment. If the bacteriuria is unaccompanied by symptoms the need for treatment requires further justification. Thus the significance of asymptomatic bacteriuria must be judged from its natural history, and this differs according to the context in which it is diagnosed.

Between 3 and 7% of pregnant women are found to have bacteriuria at their first attendance at the antenatal clinic. Untreated, between 25 and 40% of these patients will develop acute pyelonephritis during pregnancy. Eradication of the bacteriuria by antimicrobial treatment prevents these attacks, and hence it is now generally considered worth while diagnosing and treating asymptomatic bacteriuria in pregnant women. Some studies have raised a suspicion that there is a higher risk of prematurity and perinatal mortality in women with bacteriuria but this has not been generally confirmed. Long-term follow-up has shown that recurrences of bacteriuria are common in patients with previously infected urine. In patients in whom the bacteriuria has proved difficult to eradicate and in those who have developed acute symptomatic pyelonephritis—that is, with loin pain and rigors—radiological abnormalities are common. The overall incidence of radiological abnormalities in patients discovered to have bacteriuria of pregnancy and investigated after the pregnancy is between 20 and 50%, being higher (for some reason which is not understood) in Melbourne and in Texas than in London. There is no evidence that these radiological abnormalities are caused by infection during pregnancy, and probably in adults calyceal clubbing and cortical scarring precede rather than follow the attacks of acute pyelonephritis.

Though the incidence of asymptomatic significant

bacteriuria in non-pregnant women has not been so intensively studied, it is probably similar to that found at the antenatal clinic. The incidence of symptomatic infections among these patients is also similar, but the infections are much less severe. The value of treating asymptomatic bacteriuria in non-pregnant women has been questioned. Reinfections with different organisms appear to be more likely to be associated with symptomatic infections than is the original untreated bacteriuria. Spontaneous remission of the bacteriuria occurs in patients in whom there are no radiological abnormalities.

Asymptomatic bacteriuria is found in 1 to 2% of school-girls. Further questioning of the parents of these children may show that the significance of symptoms of enuresis, frequency or urgency of micturition, or of obscure fevers had not been appreciated. The intravenous pyelogram shows pyelonephritic scarring in at least one in ten, and hence radiological pyelonephritis is likely to be present in one out of every 500 schoolgirls, which makes it the most common renal disease of children. Nevertheless, long-term antimicrobial prophylaxis in children with known vesico-ureteric reflux may permit normal renal growth and prevent the development of renal scars.

The risks associated with finding bacteriuria in various situations will be better defined when the results of long-term prospective studies are available. Bacteriuria cannot be equated with infection of the host. Pathogenic organisms may be carried in the throats and colons of certain people without causing disease; possibly an analogous situation exists among persons with bacteriuria, but, unlike the throat and colon, urine does not have a normal flora.

Localization of Infections

Quantitative bacteriology allows the precise diagnosis of significant bacteriuria but does not indicate whether the infection is confined to the lower urinary tract or involves the kidneys. There is a great need for a simple and reliable test which will permit this differentiation to be made, for proof of renal involvement has a profound influence on the management of individual patients. At present various interesting approaches are being used to investigate this problem.

Direct proof of upper urinary tract infection can be obtained by the following:

Bacteriological Culture

Ureteric Urine.—Ureteric catheterization is the only method which also permits the site the infection involves to be determined. This technique carries a risk of surgical trauma to the ureters, but more than 200 such investigations have been performed at St. Thomas's in recent years with no complications other than transient haematuria. In 35% of these investigations the infection was confined to the bladder and in 65% the upper tract was involved. In one-third of the latter group infected urine was obtained from both ureters; in one-third from the right ureter; and in one-third from the left ureter. In two-thirds of the patients who had symptoms these were a correct pointer to the site of the infection.

K. H. Fairley and his colleagues have described a technique for obtaining ureteric urine which is less troublesome for the patient, and has the advantage that it can be used during pregnancy. By means of a Foley catheter the bladder is sterilized with a solution of neomycin and a fibrinolytic enzyme. Following a washout with sterile water the urine entering the bladder is collected at three ten-minute intervals. A rapidly rising bacterial count in these samples indicates infection of the upper tract.

Renal Biopsy.—Because of the patchy nature of pyelonephritis interpretation of the results of culture of renal biopsy material is difficult.

Indirect Evidence

Evidence of renal involvement may be sought by the following indirect approaches:

Microscopy of the Urine.—Rarely this may reveal granular or leucocyte casts, which are said to be dependable evidence of renal involvement. An increase in white cell excretion rate may be provoked by the intravenous injection of 40 mg. prednisone in patients with pyelonephritis. Unfortunately, a similar increase may also occur in patients with inflammation of other tissues, such as prostatitis. "Glitter" cells have been thought to indicate pyelonephritis, but they may be found in any case with pyuria when the urine is hypotonic. The Brownian motion in the cytoplasm of these pale, swollen leucocytes from which they get their name is related to the osmotic pressure of the urine.

Maximal Urinary Concentrating Ability.—A defect in concentrating ability has been shown in patients with both symptomatic and asymptomatic bacteriuria. This may sometimes be improved after effective treatment. This test, like any which demonstrates a defect in renal function, is non-specific so far as the cause of the renal damage is concerned.

Serum Antibody Titre.—A serological approach, using a simple agglutination procedure with the patient's organism as antigen, has provided a new method for diagnosing renal involvement. A close relation between infected ureteric urine and a significantly raised serum antibody titre has been shown, though infection of other tissues, such as prostatitis, may also cause a rise in antibody titre.

Pyelonephritis

In the presence of the typical clinical history, physical signs, and laboratory evidence of bacterial infection of the urine the diagnosis of acute pyelonephritis may be made with some confidence. The pathological changes in the kidney at this time probably include any of the appearances which have been described at necropsy in patients dying with acute pyelonephritis. This is a patchy disease, and appearances may range from fairly diffuse involvement of the medulla, with microabscess formation, to localized wedge-shaped lesions.

How often do multiple subclinical attacks of acute pyelonephritis occur? How often do these progress to chronic pyelonephritis, with progressive destruction of renal tissue? How often is bacterial infection the chief initiating or accelerating aetiological factor in producing the scarred, contracted "end stage" kidney? The answers to these questions are conjectural. Most pathologists regard the macroscopic appearances of calyceal distortion with overlying coarse scarring as indicative of pyelonephritis. Nevertheless, it is now widely admitted that histological findings in necropsy or in renal biopsy material are not on their own sufficient to diagnose chronic pyelonephritis if by this is meant, as is usually the case, chronic bacterial infection of the kidney. The microscopic features which have previously been interpreted as representing chronic nonobstructive pyelonephritis include the following: a chronic interstitial inflammatory reaction with lymphocytes and plasma cells; tubular atrophy and dilation with "colloid casts"; and relatively well-preserved glomeruli which often show periglomerular fibrosis and the effects of ischaemia. It has been said that the disease is "active" when polymorphonuclear leucocytes are found in the interstitium or in tubular lumina; otherwise the terms "inactive" or "healed" have usually been applied.

It is now clear, however, that renal disease associated with the histological appearance of "active" nonobstructive pyelonephritis according to the strictest of criteria, may occur and progress in the absence of any evidence of infection of the urinary tract. Since direct evidence of bacterial infection

is not always present, it has been postulated that certain cicatricial changes may cause progressive renal damage after the acute bacterial phase has subsided. Exacerbation of renal damage might be due to bacterial toxins, immunological insults, or ischaemia. But it is often difficult to conclude that ischaemic changes are a secondary and not a primary event. And it is not easy to exclude other noninfective factors which may also lead to the appearances of "interstitial nephritis." The histological appearances are more reliably interpreted if their differential diagnosis is recalled. Noninfective injury which may cause the histological changes of interstitial nephritis includes the following: hypokalaemia; nephrocalcinosis; hyperuricaemia; hypertensive vascular disease; obstruction; x-irradiation; congenital renal dysplasia, particularly in infancy and childhood; ageing; and damage due to drugs, notably phenacetin. Injury due to any of these events is likely to predispose to secondary bacterial infection. It is therefore not fair to expect the pathologist to unravel the pathogenesis of the "end-stage" kidney. For his part, it may be wiser in describing the pathological changes to employ the words "interstitial nephritis" with no connotation of aetiology.

The clinical diagnosis of chronic pyelonephritis attains a high probability if a combination of a history suggestive of upper urinary tract infections with bacteriuria, pyuria, and impaired renal function is found together with a condition known to predispose to pyelonephritis such as urinary obstruction or vesico-ureteric reflux. The diagnosis is suggested if the intravenous pyelogram shows inequality of size and irregularity of the outline of the kidneys with localized caliectasis and cortical narrowing. These radiological findings almost certainly indicate childhood pyelonephritis. Attacks of acute pyelonephritis occurring in adults have been shown to result in a reduction in the length of the affected kidney, but the evolution of scarring and calyceal changes is rarely observed.

The Diagnostic Problem

Significant bacteriuria has precise meaning. When it is found together with symptoms suggesting infection of the urinary tract it is possible to talk in terms of diseases—cystitis and pyelonephritis. Nevertheless, important infections in the urinary tract may be asymptomatic and they can only be poorly localized from their symptomatology. Interstitial nephritis describes pathological changes in the kidney that may be wholly or partly the result of bacterial infection, but that may also be the result of noninfective injury. Proof of renal involvement in infections of the urinary tract rests at present with techniques which are not generally available. Such proof can never be construed as indicating that bacterial infection is either the primary or the only mechanism damaging an individual patient's kidneys. But it does offer a rationale for treatment and for the prevention of progressive renal damage.

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