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Abstract
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In a short article it is only possible to outline the important advances in our knowledge of the serious and often fatal disease—pyelonephritis. This pathological entity has been well recognised since the nineteenth century but interest in its clinical aspects has only been aroused since the end of the second world war. Prior to this little attention was paid to pyelonephritis by clinical workers until the classical paper of Longcope (1937). The disease is very protean in its presentation which makes a clear definition of the term pyelonephritis difficult. Acute or chronic pyelonephritis may arise in normal kidneys by infection with micro-organisms or in kidneys structurally altered by prior disease processes or congenital malformations.

PATHOLOGY

An admirable review of the high incidence of pyelonephritis found post-mortem, undiagnosed in life in most cases and the direct cause of death in some, has recently been published (Kleeman *et al*, 1960). Further, Danish statistics demonstrate that the mortality in females from pyelonephritis has shown a steep apparent increase since 1935 (Mosbech, 1960). Gram-negative infection of the female urinary tract is notoriously common and acute disease caused by such infection may have been controlled to some extent by the introduction of sulphonamide and subsequent antibiotic therapy. Latent infection, however, may either have gone untreated or the treatment was only partially effective, leading to chronic inflammatory renal disease and ultimate death in many cases. When there is any form of obstruction to the urine outflow tract there is a much increased tendency to the development of pyelonephritis. Discussion of the disease process in the elderly male with prostatic hypertrophy is not intended here.

Acute pyelonephritis is characterised by minute scattered areas of acute polymorphic exudate in the intertubular interstitial spaces, few in number in the early case but steadily increasing with recurrent attacks of infection. If the disease progresses towards chronicity there is a steady diminution in glomerular tissue with marked renal fibrosis, atrophy and dilatation of the tubules as seen in Figure 1. Pyelonephritis is usually bilateral with one kidney more grossly affected than the other.

ETIOLOGY

Text-book descriptions of the etiology of urinary tract infection and subsequent pyelonephritis suggest three theories: the carriage of organisms by the blood stream from the colon to the renal substance; ascending infection from the bladder mucosa by the peri-ureteric lymphatics; or direct spread of organisms from the bladder via the ureteral lumen to the renal calyces. Experimental work has attempted to reproduce the disease in animals by similar routes (Vivaldi *et al*, 1960) and the bulk of evidence suggests that the third contention of direct spread of infection from the bladder via the ureters to the kidney is the commonest route of infection. In human females the

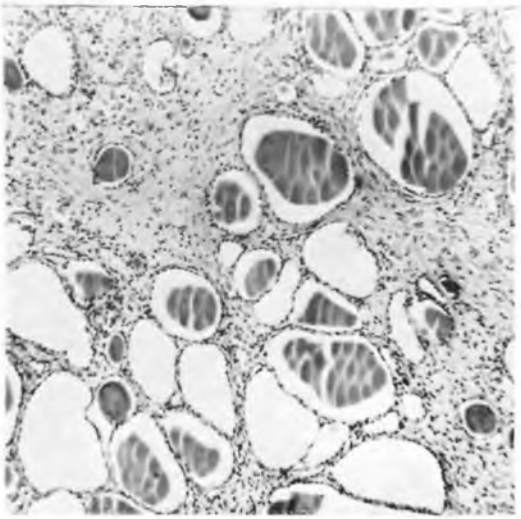

Figure 1.

Section of kidney removed from a 42-year-old multiparous female with a history of recurrent attacks of so-called pyelitis dating from her first pregnancy 19 years previously. This shows total absence of glomerular tissue and marked intertubular fibrosis with chronic inflammatory exudate throughout the field. There is striking dilatation of the tubules with atrophic epithelium. Colloid is seen in the tubular lumen — the so-called thyroid-like appearance characteristic of chronic pyelonephritis.

anterior urethra is normally colonised by gram-negative micro-organisms. Should these gain access to the bladder the urine is an excellent nidus for their rapid multiplication. If vesico-ureteric reflux mechanisms co-exist, and it is known that they are common from birth onwards, the organisms will be rapidly forced up one or both ureters to the kidneys themselves. Gross disturbance of vesico-ureteric function occurs in pregnancy, a fact known for almost thirty years (Baird, 1936).

Escherichia coli is by far the commonest single infecting organism, being present alone in about 80 per cent of most published series. Other infecting species are proteus, pyocyanea, enterococci and *staphylococcus aureus*, which are not usually found in the urinary tract in the absence of a history of bladder instrumentation. The urethral catheter was frequently passed during labour and in the puerperium until recent times. It can now be stated that catheterisation is neither necessary nor desirable for the purpose of obtaining urine for bacteriology. Catheterisation for therapeutic reasons must be carried out with scrupulous antiseptic techniques to reduce the incidence of bladder infection to a minimum (Gillespie *et al*, 1962). There is a correlation between urinary tract infection and the subsequent development of pyelonephritis, depending upon age and sex with young females predominating (Burke, 1961); with the development of active sexual life and particularly with pregnancy; with other disease processes, especially diabetes mellitus (Kalliomake and Kasanen, 1960); and with congenital malformations—most commonly found in the genito-urinary tract. All patients developing a urinary tract infection will not necessarily go on to develop chronic pyelonephritis. At present, however, it cannot be prognosed as to which idividual will do so, since the immune mechanisms of pyelonephritis are very imperfectly understood (Beeson, 1955; Guze, 1961). In Edinburgh a large scale investigation of pregnant women has been undertaken in the past three years. Significant urinary tract infection has been found in seven per cent. of primiparous women rising to over 20 per cent. in multipara. These findings correlate closely with the work of Kass in the United States (Kass, 1959). In schoolchildren the incidence of urinary tract infection is much higher in females than in males (Kunin *et al*, 1962; Kunin and Halmagyi, 1962). Despite these findings, however, pyelonephritis is not invariably detectable in such patients. Indeed, the true incidence of urinary tract infections in the community as a whole is at present unknown but there is no doubt that they are common and not infrequently associated with renal disease. Long-term prospective studies must continue for many years to come if the problem of pyelonephritis is to be elucidated.

CLINICAL FEATURES

The classical features of acute and chronic urinary tract infections are well known and will not be described further. As with so many other disease syndromes these probably account for only a minority of patients with infection of the urinary tract. For example, it is already known that pregnant women with significant bacteriuria are asymptomatic or have mild urinary symptoms wrongly attributed to the effect of the pregnancy. Some of these women will develop classical so-called acute pyelitis of pregnancy but by no means all will do so. About half of the infected pregnant women will still show evidence of persistent infection without

symptoms after delivery. For these reasons the concept of screening urine for asymptomatic infection during pregnancy as a routine measure is becoming acceptable and it might be forecast that this will become just as much a routine examination as the chest radiograph or Rhesus factor estimation at the present time.

Female infants who show failure to thrive with episodes of unexplained fever, irritability, vomiting or diarrhoea should have the urine adequately cultured for evidence of infection. In the author's own experience approximately 50 such infants per year are referred to hospital with various diagnostic labels such as feeding upset, pyrexia of unknown origin or gastro-enteritis. Unexplained hypertension in middle-aged women should lead to investigation of the renal tract for evidence of pyelonephritis and latent infection. The urine should be regularly cultured as a routine measure in female diabetics. Chronic renal infection should be suspected in post-menopausal women with apparently unexplained refractory anaemia which has failed to respond to iron. Such anaemias are not necessarily associated with uraemia even when chronic pyelonephritis is moderately or well advanced. The one important symptom which can be looked upon as highly suspicious of chronic renal tract infection is nocturia. Impairment of tubular function leads to failure in the concentrating power of the kidneys and it is already known that many women, especially multipara, come to accept recurrent nocturia as their norm. This symptom will not be revealed, therefore, unless the patient is questioned directly. As a result of the nocturia continuous interruption of normal sleep will lead to general vague symptoms of daily tiredness, irritability and lassitude which may be wrongly attributed to other causes such as the menopause or domestic anxiety. The eradication of infection in such women often leads to reduction or abolition of night rising and so to prolonged sound sleep with great improvement in general health.

The clinician must be aware of the common occurence of chronic urinary tract infection in females at all ages with minimal symptomatology easily attributable to other processes and he should not diagnose "menopausal neurosis" or idiopathic insomia before he has excluded this important infection.

DIAGNOSIS

The diagnosis of obvious acute urinary tract infections will be confirmed by the finding of pus and bacteria in freshly voided specimens of urine (Murdoch *et al*, 1959). This will be cultured within 20 minutes of voiding or the urine should be refrigerated at 4 C until it is sent to the laboratory. There is controversy as to whether it is necessary to count the numbers of bacteria in the urine. This is a convenient measurement when the numbers exceed 100,000 per ml. which is regarded as significant of infection, while those below this figure merely indicate contamination (Kass, 1957). The presence or absence of pus cells need not necessarily influence this diagnostic criterion. If bacteria are absent some authorities advocate the estimation of white cell excretion rates in urine (Houghton and Pears, 1957; De Wardener, 1960). This tedious and time-consuming procedure is of doubtful value in the diagnosis of chronic pyelonephritis whether or not steriod

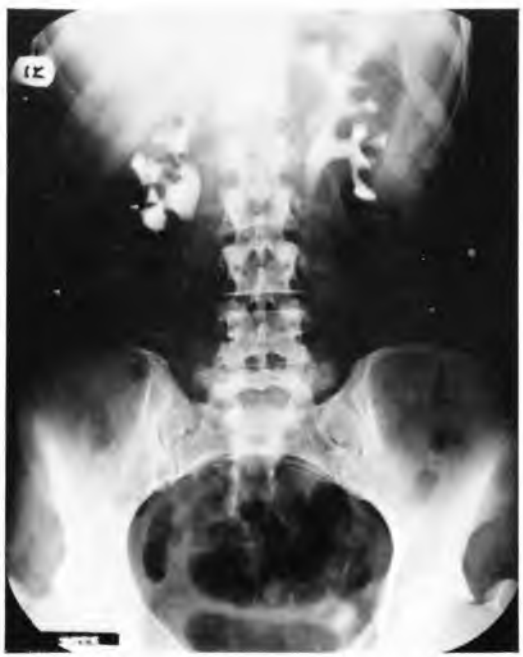

Figure 2

Intravenous pyelogram in a female aged 22 years found during her second pregnancy to have asymptomatic bacteriuria. This shows gross distortion of all calyces with characteristic "clubbing". There is marked reduction and shrinkage of the right renal cortex. The left kidney is partially hypertrophied but also shows thinning of the renal cortex in its upper pole. The appearances are typical of advanced bilateral chronic pyelonephritis.

provocation is employed and it is not advocated as a routine measure (Kennedy et al, 1963a).

When chronic pyelonephritis exists without bacteriuria radiology is valuable in establishing the diagnosis when the disease is moderately or well advanced. Figure 2 illustrates the classical radiological features of advanced bilateral pyelonephritis in a young woman. Retrograde cystoscopy and pyelography may be necessary when calculus formation or other gross surgical defects are present or suspected. Voiding cystometrograms will demonstrate vesico-ureteric reflux (Hodson and Edwards, 1960) and aortography may occasionally be an added refinement to demonstrate vascular anomalies such as renal artery stenosis. Standard tests of renal function will usually be undertaken but these will have to be supplemented by more refined techniques when unilateral or bilateral surgery is contemplated. In large medical centres I^{131}—labelled Hippuran excretion is being used to estimate individual kidney function more accurately. These refinements should not usually be necessary in the early case without obvious disease of the renal cortex and this is when the clinician would prefer to diagnose pyelonephritis in order to obtain full clinical and bacteriological cure. Because the disease is so patchy percutaneous renal biopsy is unlikely to be successful in diagnosing pyelonephritis. The ideal time for diagnosis is in the early stage of renal infection long before impairment of renal function can be detected by the crude techniques at present available. The clinician must learn to suspect the presence of a urinary tract infection in young women or children with vague ill-health. This will lead to urine culture which is almost invariably positive in the early stages of the disease. The differential diagnosis should not be difficult but if the urine is sterile renal tuberculosis must be excluded by appropriate culture. Other inflammatory renal diseases presenting with pyuria or haematuria should be readily excluded by other methods. Pyelonephritis is the commonest renal disease encountered in European and North American women.

TREATMENT

The treatment of urinary tract infections must be considered in two groups: first, the acute infection, and second, the chronic relapsing case.

The acute infection will most frequently be encountered in general practice where facilities for accurate diagnostic bacteriology will not always be readily available. The clinician can reasonably assume that the infecting organism will be *E. coli* in over 80 per cent of his patients. At the same time it is important for him to realise that these micro-organisms, even in general practice, will not invariably be sensitive to the sulphonamides. Recent studies in Edinburgh have shown that about 25 per cent of strains of E. coli from general practice sources are sulphonamide-resistant. Despite this many practitioners still elect to use a sulphonamide for the first acute infection even although there is a 25 per cent. chance that this treatment will be unsuccessful. Further objections to using the sulphonamides as drugs of first choice in this field are that they are bacteriostatic, acetylated in the liver, protein-bound and do not appear in urine in high concentration, especialy if this is diluted by "forcing fluids" during treatment. There is the added risk of marrow toxicity, especially if long-acting sulphonamides are given for prolonged periods. Chloramphenicol has obvious disadvantages and should not be used at all. The tetracyclines are bacteriostatic and many *E. coli* strains are tetracycline-resistant in the general population. During the past year it has been shown that the tetracyclines cross the placental barrier readily and are deposited throughout the foetal skeleton. Thus it would seem unwise to give tetracyclines for urinary tract infections in pregnancy. The novobiocin and tetracycline combination is even more toxic and should not be used. Streptomycin is bactericidal for many *E. coli* strains but it must be given in the presence of a continuously alkaline urine—this is almost impossible to achieve in general practice. Nitrofurantoin has enjoyed a popular reputation but it is interesting to speculate as to how many patients genuinely take this drug because of its capacity to produce heartburn and nausea even in moderate therapeutic doses. Recent reviews now indicate that more serious neurotoxicity and marrow toxicity can be produced by nitrofurantoin, especially if it is given for prolonged periods. The ideal drug for the acute infection should be one which is bactericidal, uniformly absorbed from the gut after oral administration, giving high tissue and urine concentrations without toxicity. Such a drug does not exist but cycloserine comes nearest to these theoretical requirements. A dose of 250 mg. twice daily for 14 days will eradicate 95 per cent. of *E. coli* infections provided renal function and structure are normal (Syme *et al*, 1961). Cycloserine is toxic to the nervous system, producing drowsiness, psychosis and even epileptiform convul-

sions if high blood and tissue levels arise as a result of impaired renal function. This is unlikely in the acute uncomplicated case but the drug should be withdrawn at the first sign of drowsiness—a toxic effect which is more easy to detect than, for example, bone marrow depression. Furthermore, cycloserine toxicity is completely reversible upon withdrawal of the drug. In summary it would seem that the general practitioner will use a sulphonamide as the drug of first choice but if this drug fails to eradicate the infection cycloserine should be considered as the drug of second choice for acute *E. coli* infections.

The refractory or relapsing case presents an entirely different problem and it is important to ensure that the renal tract is fully investigated to exclude calculus, obstruction or serious renal damage before administering any drug. Accurate bacteriology, of course, must supplement these investigations. Table 1 shows the antibiotic susceptibility of a large number of *E. coli* and other common urinary pathogens in the Edinburgh area studied over the past

mined by such factors individually. Newer antibacterial drugs are now available for the eradication of most pathogens encountered in the renal tract. Cycloserine is suitable for 95 per cent. of *E. coli* strains. 250 mg. twice daily will eradicate the organism and after 14 days the dose can be reduced to 250 mg. on alternate evenings for indefinite periods of time, depending upon the presence of radiological pyelonephritis or, for example, vesico-ureteric reflux. Some patients in Edinburgh have been taking suppressive cycloserine for up to three years with excellent bacteriological results. The relapse rate in a large series of patients is only five per cent. This compares very favourably with relapse rates of around 30 per cent. in other series treated with sulphonamides, nitrofurantoin or mandelic acid. Cycloserine can also be given during pregnancy either for short courses or throughout the pregnancy. Studies of foetal cord blood and amniotic fluid after delivery in patients treated with this drug show that very little of the antibiotic crosses the placental barrier. Cycloserine seems to be the

Organism	No. of Isolates	% strains RESISTANT in vitro to:					
		Su.	S	C	T	Novo. + T	NitroF.
E. coli	495	66	32	8	89	98	4
Proteus spp.	71	88	29	15	100	100	74
Klebsiella	30	67	27	10	73	—	17
Ps. pyocyanes	30	100	100	90	93	—	100

Antibiotic sensitivity of urinary tract pathogens (Disk-Diffusion Method).

three years. In hospital, to which the refractory case eventually comes, the older and more traditional drugs do not show *in vitro* effectiveness except in a small number of the isolates. The treatment of such cases is not simply the administration of an antibacterial drug based on *in vitro* susceptibilities. Drainage defects must be corrected surgically, calculi must be removed where possible and nephrectomy, partial nephrectomy or bilateral partial nephrectomy may be required to remove non-functioning areas of renal tissue before any drug can be expected to eradicate the infection. The management of each case will be deter-

antibiotic of first choice for prolonged suppressive therapy in patients suffering from established chronic pyelonephritis or in young females who have demonstrable vesico-ureteric reflux. At present it is impossible to say for how long the drug should be given but it would appear indicated until such time as the reflux has disappeared or indefinitely to patients who have only very little functioning renal tissue.

As will be seen from Table 1 proteus and klebsiella strains are resistant to standard forms of treatment. For fulminating infections with these organisms, with or without septicaemia, the antibiotic of first choice is kanamycin

sulphate given in a dose of 0.25 G. 6-hourly intra-muscularly for 14 days (Murdoch *et al*, 1962). The indications and contra-indications for the use of kanamycin sulphate have been fully reviewed recently (Murdoch, 1962). *Proteus mirabilis* strains are not infrequently fully sensitive to the action of ampicillin which is, therefore, suitable for the treatment of acute infections with this organism in a dose of 500 mg. 6-hourly for 14 days. Prolonger suppressive treatment with this antibiotic can be given in a dose of 250 mg. on alternate days (Kennedy *et al*, 1963b). Despite its early promise (Brumfitt *et al*, 1962) ampicillin has been disappointing in the treatment of *E. coli* and most other gram-negative urinary tract infections. *Pseudomonas pyocyanea* infections of the urinary tract are fortunately uncommon as they were in the past resistant to almost all forms of treatment (see Table 1). A close chemical relative of polymyxin B which is less neurotoxic—colistin methanesulphonate—is highly effective both *in vitro* and *in vivo* against pyocyanea infections and this antibiotic should be given in a minimum dose of 1.5 million units 8-hourly for 14 days when it will usually eradicate the infection completely (Carroll and Malette, 1961; Courtieu *et al*, 1961). A note of caution is, however, necessary when using either kanamycin or colistin in the presence of impaired renal function. Dangerously high blood levels may then occur, giving rise to ototoxicity with kanamycin and peripheral paraesthesiae or even chemical encephalitis in the case of colistin. These antibiotics should only be given in the presence of uraemia where facilities are available for monitoring the blood levels of the antibiotics daily. Blood levels of kanamycin sulphate should not be allowed to rise above 30mcg/ml. and of colistin above 64 mcg/ml. if neurotoxicity is to be avoided.

CONCLUSIONS

In recent years there has been an increasing awareness of the serious import of gram-negative infection of the urinary tract, especially in young and middle-aged females (Murdoch, 1963). In the past a casual attitude towards these infections has led to indifferent standards by which therapy has been judged. The emergence of drug-resistant pathogens has invitably occurred, especially in hospital practice, and inadequate standards of bacteriological cure have been adopted. Symptomatic cure of so-called cystitis is easy to achieve while bacteriological cure is much more difficult. This is especially the case when infection has become established in the renal parenchyma itself. In the future it is to be hoped that treatment will be judged by adequate *long-term* evidence of bacteriological cure for the acute and apparently uncomplicated case while in the patient with established pyelonephritis long-term suppressive therapy will be adopted and controlled by adequate bacteriology. In essence the prevention of pyelonephritis is a theoretical possibility while in practice it is very difficult to achieve. This should not deter the clinician of the future from ensuring that apparently trivial infections of the urinary tract are rigorously eradicated with modern bactericidal drugs and any evidence of relapse or reinfection will lead to full investigation of the renal tract to exclude "surgical' disease. If such steps are taken in the future the trend toward increasing morbidity and mortality from pyelonephritis will be reversed.

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