Urinary Tract Infection

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Since my last review[1] of urinary tract infection (UTI), there have been a number of advances that have a bearing on clinical practice.

Bacterial Adherence

Every fisherman knows that the best place to cast is at the interface of fast flowing and static water because this is where the fish lie waiting for currents to deliver their food supply. Much the same applies to bacteria growing in liquid media. They cling to solid surfaces and allow the stream, including the urinary stream, to deliver organic nutrients and remove waste products. The ability to cling to surfaces is a property shared by bacteria, viruses and fungi. When bacteria are grown on solid media they lose their stickiness and it may be that this is the reason why microbiologists, who usually grow bacteria on solid media, have tended to under-estimate the importance of bacterial adhesion. Adherence is a vital first step in the colonisation of mucosal surfaces and pathogenic bacteria possess several adherence mechanisms ranging from the sticky polysaccharide capsules of pneumococci to the web of polysaccharide fibrils of dental plaque and caries producing streptococci. Entero- and uro- pathogenic bacteria rely on the possession of fine proteinaceous fibrils known as fimbriae (Fig. 1).

![Fig. 1. Electron micrograph of Esch. coli showing fimbriation.]

The importance of fimbriae in the pathogenesis of gonococcal[2] and gastrointestinal infections[3] is undoubted. There is a growing body of evidence that they are involved in the early stages of urinary tract infections. *Esch. coli* strains that produce UTI cling to uroepithelial cells more than to commensal faecal strains[4] and heavily fimbriated *Esch. coli* show greater adherence to uroepithelial cells and persist longer in experimental infections than strains with few or no fimbriae[5]. On subculture fresh isolates from cases of human UTI are nearly always fimbriated[6]. Most Gram-positive organisms do not possess fimbriae but one exception is *Corynebacterium renale*, which causes acute pyelonephritis in parturient cows[7].

Using specific antisera, several types of fimbria have been identified[8]. Not all fimbriae are concerned with adhesion. So far, two types of fimbria have been implicated in the adhesion of *Esch. coli*; these are types 1 and F7. Type 1 fimbriae adhere to d-mannose residues on the surface of the host cells and produce agglutination of guinea-pig red cells. When *Esch. coli* possessing type 1 fimbriae are mixed with urine deposit most of the organisms stick to the uromucoid (Tamm-Horsfall protein) and only a few cling to the uroepithelial cells, whereas F7 fimbriated *Esch. coli* cling to the cells and not to the mucoid[9]. It is possible that this is the reason why type 1 fimbriated *Esch. coli* tend not to produce UTI since they are easily removed from the urinary tract because the uromucoid acts as the sputum of the urinary tract. Adhesion by type 1 fimbriae is readily prevented by exposing the bacteria to d-mannose, for this sugar occupies the binding sites on the fimbiae. Urinary pathogens possessing F7 fimbiae are d-mannose resistant and produce agglutination of human red cells, except for the red cells of blood group p1-negative subjects[10]. What makes blood group p1-negative red cells different from p1-positive cells is that they lack a glycosphingolipid trihexosyl ceramide in their envelope. The receptor recognised by the F7 fimbiae in p-positive cells is the non-reducing terminal trisaccharide of this glycosphingolipid, namely α-D-galactose-β-D-galactose-β-D-glucose (Fig. 2).[11] This trisaccharide inhibits adhesion of urinary pathogens to the uroepithelium and also prevents the agglutination of p-positive human red cells by F7 fimbrated *Esch. coli*. Vaginal and periurethral cells from patients with recurrent UTI have more attachment sites for uropathogenic *Esch. coli* than cells obtained from healthy controls[12, 13]. This observation takes us one step nearer to the discovery of a genetic basis for UTI. Could it be that cell envelope oligosaccharides determine susceptibility to recurrent UTI? In veterinary practice it has been possible to breed piglets that lack attachment sites for *Esch. coli*.

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K88, which produces gastroenteritis. Such piglets are protected from this lethal disease[14]. Here we are dealing with a link between genetic make-up, bacterial attachment and susceptibility to disease. The therapeutic potential of these exciting new discoveries is clear. One would not wish to suggest that eugenic practices be adopted in an attempt to breed UTI-resistant women but what might be possible is to use oligosaccharides to block attachment of urinary pathogens to the perineal floor and so prevent perineal colonisation and recurrent attacks of UTI. Such an approach to the prophylaxis of UTI would be preferable to the long-term use of antimicrobial agents to which resistance almost invariably develops.

**Abacterial Cystitis**

In half of all patients presenting with frequency and dysuria urine culture fails to show significant bacteriuria. Before such patients are labelled as suffering from abacterial cystitis or the 'urethral syndrome', it is necessary to be certain that factors leading to a false diagnosis of the condition are excluded. These are listed in Table 1. Chief amongst them is the incorrect interpretation of quantitative urine culture. When Kass introduced the concept of significant bacteriuria[15], it was to screen apparently healthy populations for covert UTI. Unfortunately, this important contribution continues to be misunderstood, with the result that microbiology laboratories throughout the world are called upon to undertake unnecessary quantitative cultures to establish the diagnosis of symptomatic infection. The scientific basis for quantitative urine culture has been stated and re-stated in numerous publications and was reviewed recently[16]. Two points are important. First, when a carefully collected and cultured urine specimen shows a count of $\geq 10^8$ colony-forming units (CFU) per litre and is said to show significant bacteriuria, the statement is statistical; the finding of $\geq 10^8$ CFU per litre expresses a likelihood that organisms are multiplying in the bladder urine. The second aspect, which is often misunderstood, is that significant bacteriuria refers to the findings in urine specimens obtained from asymptomatic individuals infected with Gram-negative bacilli. In the presence of symptoms or when organisms other than Gram-negative bacilli are involved the confidence limits at various levels of viable bacterial count may well be quite different. Some of the factors which can greatly alter these confidence limits in symptomatic subjects are shown in Table 2. A great deal of effort and money could be saved if we ceased to undertake quantitative urine culture for the diagnosis of symptomatic infection. The diagnosis of symptomatic infection should be based on the history, together with the finding of pus cells and a pure growth of uropathogenic micro-organisms whatever their number. Some years ago it became apparent to me how rarely, if ever, a translucent urine specimen yielded a positive urine culture. To investigate this we recently undertook a study of 100 urine specimens sent to our laboratory, 79 of

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**Fig. 2.** Carbohydrate moiety of the p, glycosphingolipid which acts as the attachment site for F, fimbriated Esch. coli to human erythrocytes and periurethral cells[11].

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\alpha-D\text{-}galactopyranosyl\rightarrow(1\rightarrow4)\beta-D\text{-}galactopyranosyl\rightarrow(1\rightarrow4)\beta-D\text{-}glycopyranoside
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**Table 2.** Some factors leading to reduction of bacterial colony count.

| Physiological | Frequent voiding |
|---------------|-----------------|
| Diuresis      | Culture at inappropriate time of day |
| Lateral       | Culture at inappropriate time of day |
| Iatrogenic    | Contamination of urine with antiseptics |
| Chemotherapy  | Bacteriological  |
| Urine of poor nutritional value | Infection due to fastidious organisms, e.g. cystine-dependent Esch. coli |
| L-forms       | Anaerobic bacteria |
| Confinement of infection to urethra | Presence of bacteriophage in urine |
| Adhesion of bacteria to pus cells and/or uromucoid | Use of inappropriate culture media |

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which were judged to be macroscopically clear when transilluminated using an angle-poise lamp, and 21 of which were judged to be cloudy. None of the 79 translucent specimens were infected whereas 16 of the 21 cloudy specimens were found to have pus cells on microscopy and micro-organisms on culture. The ancient art of uroscopy is not yet dead.

It follows that abuse of the colony count has created more patients with abacterial cystitis than actually exist. The introduction of suprapubic aspiration (SPA) of urine has further reduced the number of patients with abacterial cystitis. Approximately 20 per cent of sexually active women with frequency and dysuria are found to be infected with *Staphylococcus saprophyticus* when suprapubic aspirates of the urine are cultured[17]. Prior to this discovery staphylococci had been disregarded as contaminants and now we know that treatment of the infection produces relief of symptoms. A role in the pathogenesis of abacterial cystitis has recently been claimed for microaerophilic and anaerobic bacteria which can be isolated from urine when it is incubated for 48 hours or more in an atmosphere of 7 per cent carbon dioxide[18]. Similarly, *Chlamydia trachomatis*, *Mycoplasma hominis* and *Ureaplasma urealyticum* have been implicated in the pathogenesis of abacterial cystitis[19]. It has been claimed that careful bacteriological study will reveal one or other of the foregoing causes of abacterial cystitis in more than 90 per cent of patients in whom frequency, dysuria and pyuria co-exist[20]. Although such claims still require confirmation, it is evident that the size of the problem of abacterial cystitis is diminishing.

**Dynamics of Bacteriuria**

Screening for covert bacteriuria (CB) in apparently healthy populations reveals that the condition is very common. Table 3 shows the prevalence rates of CB in different population groups. Covert bacteriuria is not a static condition but shows a constant turnover. Five per cent of the adult female population is infected at any one time. This level of prevalence remains constant even though 25 per cent of the infected population rid themselves of their infection each year[21]. These facts alone do not allow us to calculate the acquisition rate of infections because not all infected women have an equal chance of developing a spontaneous cure. In our follow-up of girls with symptomless infections which were left untreated, 22 per cent developed a spontaneous cure, mostly during the first year of the follow-up. Extrapolating from these data allows a rough estimate of the risk of a woman acquiring UTI during her lifetime because constancy of the point prevalence of infection requires an acquisition rate that equals the spontaneous cure rate. It follows that in the adult female the number acquiring infection each year would be of the order of 20 per cent of the infected population, which amounts to one in every 100 women. Over a lifetime, therefore, it would not be an exaggeration to suggest that women have at least a 50 per cent chance of acquiring infection at some stage. Fig. 3 shows the dynamics of CB. The frequencies with which the various sequelae of CB occur are not shown in the diagram because they vary considerably in different population groups and because the data are too scanty in some instances, for example, the neonate and the elderly.

One of the most important problems in UTI is to determine how often symptomless infections give rise to symptomatic infections and to what extent symptomless infections represent the submerged part of an iceberg which accounts for the high morbidity and continuing mortality of UTI. The solution to these problems holds the key to the preventive value of screening for UTI. Even if screening and treatment of CB were to offer an advantage, the high turnover of the condition in schoolgirls and adult non-pregnant women would make it impossible to put such screening programmes into practice because the whole healthy population would have to be screened repeatedly so as to bestow the advantage of screening and treatment upon all. This would place an impossible load upon the medical resources of even the most prosperous countries. From a public health standpoint screening for bacteriuria is therefore unlikely to be of value as a preventive measure. The one exception to this generalisation is bacteriuria in pregnancy because this rarely clears spontaneously and predisposes to acute pyelonephritis. Moreover, treatment, which can readily be prescribed in antenatal clinics, can prevent the development of such symptomatic infection.

Nephrologists are particularly interested in the relationship of covert infection to chronic pyelonephritis. This is still one of the most controversial subjects in the

![Fig. 3. Dynamics of covert bacteriuria.](image-url)
field of UTI. Until recently, the prevalent view was that untreated or inadequately treated UTI progressed slowly and often silently to kidney scarring, hypertension and renal failure. It is now apparent that in adults, at least, such a progression is an extremely rare occurrence. Prospective studies of the natural history of UTI in adult women and men have shown that, in the absence of complicating factors such as diabetes, analgesic nephropathy or obstructive uropathy, UTI is a benign condition. Retrospective studies confirm this. Women from whom a past history of UTI was obtained showed no difference in urine concentrating power, serum creatinine or blood urea when compared with age-matched controls who did not have a past history of UTI. There was one important exception to this, namely women in whom the past history of UTI could be traced to the childhood period. Here was the first evidence which suggested that damage due to UTI has its origins in childhood. Further indications that this might be the case came from the observation that adults with UTI and damaged kidneys more often dated the onset of their symptoms to childhood than patients in whom infection occurred in the absence of kidney damage (for review see reference 22).

In several surveys of UTI in children it has been shown that 25 per cent of the infected subjects have coarsely scarred kidneys. In childhood about one-third of infected children show vesico-ureteric reflux (VUR), the severity of which was closely associated with the presence of kidney scarring, scarring being most common in kidneys drained by severely refluxing ureters. The reason for this association has been the subject of much debate. VUR facilitates ascent of organisms to the kidney, creates residual urine, thus enhancing bacterial multiplication, and may produce kidney damage by a water hammer or ‘Severn Bore’ effect. It is now clear that new kidney scars rarely develop after the age of four and that they nearly always develop in areas in which intra-renal reflux (IRR) due to pyelotubular backflow can be demonstrated on micturating cytography[23].

**Kidney Scarring**

Studies of the natural history of UTI have been much concerned with the development of kidney scars. The effect of the infection upon kidney function has been relatively neglected, yet ultimately it is reduction of glomerular filtration rate which threatens life. Little is known of the mechanism whereby an apparently healthy child with a coarse pyelonephritic scar in one or other pole of the kidney progresses insidiously to chronic kidney failure in later life. The mechanisms which may play a part in this progression are as follows.

**Infection**

In childhood, UTI when associated with VUR and IRR produces both kidney scars and impairment of kidney growth; the cause of the growth failure is still uncertain. In experimental models compensatory growth after unilateral nephrectomy is greatly impaired by renal infection and the impairment of compensatory growth can be prevented by immunisation against the O antigen of the infecting strain of *Esch. coli*[24]. This finding suggested that bacterial endotoxin was responsible for the growth failure associated with ascending infection. Our observations on 5-11 year old schoolgirls with covert bacteriuria followed-up for 4 years, showed that 10 per cent developed progression of pre-existing kidney damage with extension of pre-existing scars and/or failure of kidney growth[25]. This progression was particularly noted in girls with persistent infection in whom changes in the serotype or bacterial species of the urinary pathogen were observed[26]. This suggests that prevention of growth failure and of progressive kidney scarring might require long-term treatment to prevent re-infections. The painstaking work of Dr Jean Smellie has shown that such long-term prophylactic treatment given to children with symptomatic UTI does restore kidney growth to normal and can also prevent extension of kidney scarring[27]. Whatever the precise mechanism of the failure of kidney growth, it contributes to the development of kidney failure because, as the child grows, the ratio of kidney to total body weight declines and its small kidneys become inadequate to cope with the metabolic load of a fully grown subject.

Another way in which UTI can contribute to progressive kidney damage is by the development of kidney stones; this is particularly likely when the infecting organisms produce urease, as do most Proteus strains, some staphylococci and *Streptococcus faecalis*. Urease splits urinary urea, with release of ammonia, which in turn traps hydrogen ions and so raises urinary pH. In consequence, crystal deposition is encouraged, particularly as the clumps of bacteria themselves act as a nidus for crystallisation. The stones are nearly always of the triple phosphate type, i.e. calcium, ammonium and magnesium phosphate. The presence of stones usually makes it very difficult to eradicate infection for, though the surface of stones can be sterilised, organisms in the centre survive and infection recurs as soon as antimicrobial treatment is stopped. Even after surgical removal of stones infection is still difficult to eradicate because microliths often remain behind. The introduction of urease inhibitors, such as acethyrdroxamic acid, to treatment holds out promise of the prevention of urolithiasis when infection due to urease producing organisms is present[28].

**Immune Responses**

The possibility that the immune responses to UTI may induce or add to the kidney scarring produced by ascending infection was first advanced by Angell *et al.* [29]. Using fluorescein-labelled antibodies to bacterial antigens, they demonstrated bacterial antigen in pyelonephritic scars and suggested that progression of renal damage may not require the continuous presence of viable bacteria. Bacterial endotoxin modifies the antigenicity of renal tissue so that antibody produced against the endotoxin-modified kidney antigen could result in interstitial kidney damage. Moreover, kidney tissue and some strains of *Esch. coli* possess common antigens. The combination of circulating antibodies, either with endotoxin-
modified kidney tissue or with the common antigens shared by \textit{Esch. coli} and kidney tissue, might lead to complement fixation and kidney damage, but so far there has been no evidence to support this view. In patients and experimental animals with kidney infections, the search for circulating anti-kidney antibodies has been unsuccessful. Adsorption of the circulating antibody might account for these negative findings but even when locally synthesised antibody was examined for anti-kidney antibody, no activity was found. These various observations cast doubt on the suggestion that humoral auto-immune mechanisms are involved in the pathogenesis of progressive kidney scarring (for review see reference 22). Similarly, a cellular immune mechanism appears unlikely. In a rat model of ascending \textit{Esch. coli} infection we were unable to show that neonatal thymectomy or administration of an anti-rat lymphocyte globulin had any effect on the course of the experimental infections\textsuperscript{30}. Lymphocytes isolated from acutely infected kidneys also failed to show transformation on exposure to mitogen and bacterial lipopolysaccharide, whereas the circulating lymphocytes from the same animals do show blast transformation\textsuperscript{31}. This suggests that the lymphocytes present in and around pyelonephritic scars are ‘null’ cells and that they may not be involved in the pathogenesis of kidney scars by the release of lymphocytokins.

In contrast, evidence for a pathogenetic role of cell-mediated immunity has been obtained in chronic \textit{Strep. faecalis} infections of the rat kidney. Lymphocytic infiltrates and kidney scars were observed in normal rats after they had been joined in parabiosis to rats with treated streptococcal pyelonephritis of seven months’ standing\textsuperscript{32}. To date this is the only evidence suggesting a role for cellular immunity in the development of kidney damage associated with infection but it must be admitted that the possible role of macrophages in the pathogenesis of kidney scars has not been explored. This is surprising since macrophages are known to produce fibrogenic factors after ingestion of various macro-molecules.

Proteinuria in excess of 1 g per day is almost invariably present in children with chronic pyelonephritis whose kidney function declines. This would suggest the presence of a glomerular lesion. Such glomerular lesions were described many years ago—the so-called ‘alterative glomerulitis’\textsuperscript{33}. More recently, immune deposits have been found in the glomeruli of some patients with coarse kidney scars, VUR and renal impairment. It has been suggested that these glomerular lesions result from release of kidney antigens into the circulation as a consequence of back pressure damage produced by VUR. Entry of kidney antigens into the circulation might elicit an antibody response and the resulting immune complexes might then be deposited in the glomeruli. So far, searches for circulating immune complexes in patients with coarse scarring, VUR and renal failure have yielded negative results (for review see reference 34).

\textbf{Hypertension}

An association between hypertension and UTI has long been known to exist. In an uncontrolled study, 37 per cent of a group of 192 patients with chronic pyelonephritis were found to have diastolic pressures in excess of 100 mm Hg. At follow-up one to eleven years later, the frequency of hypertension in the group had increased to 65 per cent\textsuperscript{33}. These data leave little doubt that chronic pyelonephritis and hypertension are associated, but the nature of the association is not clear. There are three possibilities, first, UTI may lead to a rise of blood pressure; second, the underlying renal disease may predispose both to rise of blood pressure and infection, and third, high blood pressure may increase susceptibility to infection. Most investigators have postulated that infection produces kidney damage which in turn leads to hypertension. The most compelling evidence in favour of this suggestion is that removal of a single chronic pyelonephritic kidney from patients with hypertension has on a number of occasions resulted in the cure of their raised blood pressure. Comparison of bacteriuric with nonbacteriuric populations reveals that blood pressure is higher in the infected population\textsuperscript{36}. It is most important to recognise this association between raised blood pressure and UTI, as control of the raised blood pressure slows deterioration of kidney function. Moreover, a knowledge of the association between kidney infection and hypertension should forewarn practitioners that rise of blood pressure is more likely to occur when women suffering from UTI are started on oral contraceptives or become pregnant.

\textbf{Back Pressure}

Back pressure due to VUR may contribute to the progression of kidney damage. Urodynamic studies on subjects showing progression of kidney damage in association with UTI and VUR show that extremely high intravesical pressure of up to 150 cm of water or more may be generated during unco-ordinated detrusor contraction; such contractions are frequent in girls with UTI and VUR\textsuperscript{37}. The radiological appearance on micturating cystography in some children with VUR who develop kidney failure, strongly suggests that back pressure atrophy has played a major part in the pathogenesis of the kidney failure, in that the kidneys appear hydro-nephrotic. Back pressure might also contribute to the progression of kidney damage by causing extrusion of tubular Tamm-Horsfall protein into the renal interstitium which in turn produces a marked inflammatory response and interstitial fibrosis\textsuperscript{38}. The importance of each of these mechanisms by which focal pyelonephritic scars and kidney failure are interrelated is not known. It seems likely that there is a considerable case-to-case variation in their relative importance, underlining the need for careful assessment of each patient followed by tailor-made treatment.

\textbf{Progress in Treatment}

Two aspects of treatment have been particular subjects of discussion during the last few years. The first concerns the duration of treatment and the second the controversy regarding the use of trimethoprim alone instead of the combination of sulphamethoxazole and trimethoprim.
Treatment of uncomplicated UTI usually consists of courses of antimicrobial agents given for periods of 5 to 10 days. There is no convincing evidence that longer courses are more successful than short courses of treatment. Sterilisation of the urine by an antimicrobial agent to which the organism is sensitive is usually achieved within 24 hours of the start of treatment; if this is not achieved, the organism is likely to persist[39].

From these observations it would appear that even a single dose of antimicrobial agent could eradicate uncomplicated urinary tract infections. The earliest report of such single dose therapy was by Gröneberg and Brumfit[40], who showed that a single dose of 2g of the long-acting sulphonamide sulphamethoxine was as effective as a seven-day course of ampicillin 500 mg eight-hourly in 50 non-pregnant women. The possibility that antimicrobial agents with a shorter half-life than that of sulphamethoxine might also be effective in single doses was suggested by Brumfit and his colleagues[41] and in the last four years the efficacy of single dose therapy in UTI has been established both in children[42] and in adults[43]. Localisation studies of UTI using the bladder washout procedure[44] and the antibody coating method[45] have shown that kanamycin sulphate, amoxyccillin and cotrimoxazole in single oral doses eradicated lower tract infections in almost all cases[46], whereas upper tract infection persisted or recurred. Single doses of cotrimoxazole or amoxyccillin have been shown to be curative in 85-90 per cent of patients with normal intravenous urograms and in 50 per cent or less of those with abnormal radiological findings[47, 48]. It has even been suggested that failure of single dose therapy should be an indication for further investigation and that recurrence of infection following single dose therapy is a good method of locating UTI[49]. It would seem, therefore, that single dose therapy of uncomplicated lower urinary tract infection in the absence of radiological abnormality is highly effective and that such treatment can now be advocated, provided that careful bacteriological follow-up is carried out.

Trimethoprim on its own is now available in Britain for the treatment and prophylaxis of urinary tract infections. When first marketed in 1969, the combination of sulphamethoxazole and trimethoprim was advocated for a number of reasons. First, the combination showed greater antibacterial activity than the individual components; second, the combination therapy minimised the risk of acquired resistance to each one of the components, and third, the combination had a cidal effect rather than the static effect of its components. All of these claims have now been challenged. Trimethoprim is considerably more active than sulphamethoxazole against most bacterial species, and in the treatment of UTI there is now a good deal of evidence that the activity of trimethoprim is so dominant as to be almost entirely responsible for the effectiveness of cotrimoxazole[47]. Several observations cast doubt on the need for combination treatment. Cotrimoxazole is highly effective in many sulphonamide-resistant infections. The renal handling of the trimethoprim and sulphonamide components of cotrimoxazole are different, with the result that the ideal ratio of sulphonamide to trimethoprim of 20:1 for synergistic effect is only rarely obtained in the urine. This is because the excretion of the sulphonamide component of the drug is largely pH dependent, whereas the excretion of the trimethoprim part is flow-rate dependent[50]. It is for this reason that under different conditions of urine flow and urinary pH the ratios of sulphonamide to trimethoprim vary from anything between 1:1 to 100:1 and yet despite this cotrimoxazole is found to be effective. It follows that, at least as far as the urinary tract is concerned, there can be little justification for the continued use of cotrimoxazole, for most of the toxicity that relates to the combination therapy can be traced to the sulphonamide component. The only possible justification for continuing to use the sulphonamide-trimethoprim combination in the treatment of urinary tract infection would be if the addition of sulphonamide prevented the emergence of trimethoprim-resistant strains. Although the proportion of pathogens sensitive to trimethoprim has remained high despite increasing use of cotrimoxazole[51], in hospital practice trimethoprim resistance has shown an increase from 9.5 per cent in 1975 to 12.0 per cent in 1977[52]. This suggests that sulphamethoxazole has not effectively prevented the development of trimethoprim resistance. This is not surprising, as more than half of hospital Gram-negative bacilli are already resistant to sulphonamide and are therefore exposed to trimethoprim alone even when combination therapy is used. Most experience of the use of trimethoprim alone in the treatment of UTI comes from Finland. From there comes the disquieting report that trimethoprim resistance is found in 20 per cent of urinary pathogens isolated in out-patients and in 40 per cent of isolates obtained from in-patients[48]. Effectiveness and lack of toxicity of trimethoprim alone make it a highly desirable agent for use in treatment of UTI, particularly for long-term prophylaxis. Since it seems likely that its widespread use would alter the pattern of trimethoprim resistance, particularly in the hospital environment, it seems wise at the present time to reserve the use of trimethoprim by itself for out-patient therapy of UTI whether it be for the treatment of acute infections or for long-term prophylaxis[53].

Addendum: We have recently shown[54] that when first isolated, the urinary pathogens from 18 patients with both upper and lower tract UTI did not adhere to either uro-epithelial or buccal cells and that all except one lacked fimbriae. Fimbriation and adherence developed after subculture in nutrient media and to a lesser extent after subculture in human urine. This observation casts doubt on the importance of fimbriate adherence as a virulence factor. It seems more likely that the importance of fimbriate adherence relates to the perineal colonisation that precedes UTI.

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