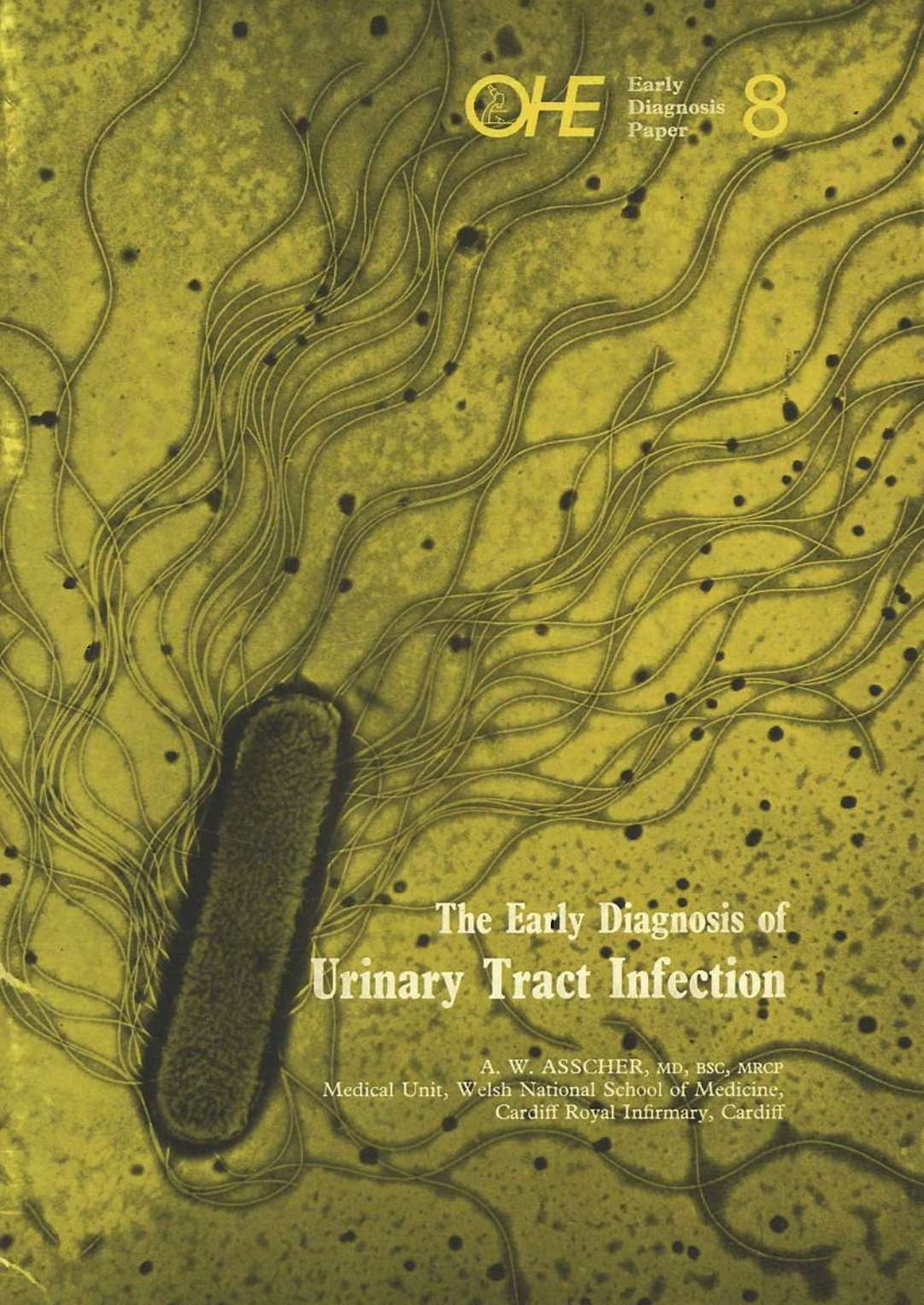

Early Diagnosis Paper 8

The Early Diagnosis of Urinary Tract Infection

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In July, 1965, the Office of Health Economics held a colloquium on Surveillance and Early Diagnosis in General Practice at Magdalen College, Oxford. It was apparent from the discussion at this meeting that General Practitioners believed that if they were to act effectively in this field, they had to have clear cut information on current screening methods and the impact of early diagnosis of disease on the long term health of the patient. As a result of this view the Advisory Committee set up by the Office of Health Economics came to the conclusion that the best method of furthering this issue was to ask experts in a number of relevant clinical fields to write short papers specifically for General Practitioners.
The Early Diagnosis of Urinary Tract Infection is the eighth of these papers in the ensuing series. Other papers in the series are:

1. *The Early Diagnosis of Raised Arterial Blood Pressure*
2. *The Early Diagnosis of Visual Defects*
3. *The Early Diagnosis of Cancer of the Cervix*
4. *The Early Diagnosis of Depression*
5. *The Early Diagnosis of Ischaemic Heart Disease*
6. *The Early Diagnosis of Some Diseases of the Lung*
7. *The Early Diagnosis of Anaemia*

Two Shillings and Sixpence

Cover illustration
Electronmicrograph of proteus mirabilis by Dr D. B. Moffat of the Department of Anatomy, University College, Cardiff, and reproduced by his kind permission.

OHE Early Diagnosis Paper 8

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Urinary tract infection is probably the commonest bacterial infection. Although primary prevention is preferable to early diagnosis and treatment, in practice it is limited to the avoidance of unnecessary instrumentation of the urinary tract. Research on the defensive mechanisms of the urinary tract may widen the scope of primary prevention.

Asymptomatic infections of the urinary tract can be detected by screening for significant bacteriuria. The value of detecting these asymptomatic infections in pregnancy is well established since eradication of bacteriuria detected early in pregnancy prevents the development of acute pyelonephritis. The cost of antenatal screening for bacteriuria may well be offset by the reduction of expenditure on hospital admissions for acute pyelonephritis. The value of bacteriuria screening amonst schoolchildren and non-pregnant adult women is undetermined. Long-term follow-up studies of bacteriuric children and adults are required in order to determine whether bacteriuria leads to progressive impairment of kidney function. So far studies of this kind suggest that significant bacteriuria in the adult is in most instances a non-progressive condition. In children, however, the long-term sequelae of untreated bacteriuria may be more serious since it may lead to impairment of kidney growth and renal scar formation particularly when the bacteriuria is associated with vesico-ureteric reflux. It seems likely that renal damage due to childhood infection lays the foundation for persistent bacteriuria in the adult. A controlled treatment trial of bacteriuria in childhood is urgently needed lest hypothesis be translated into action before proof.

Introduction

Amongst the mammalian species mankind is unique in the frequency of urinary tract infection. Along with respiratory infections, infections in of the urinary tract are the commonest in the population. Detection and treatment of these infections in asymptomatic subjects is now possible and the provision of facilities for early diagnosis and treatment must be given serious consideration. No doubt remains that untreated asymptomatic infection predisposes to acute symptomatic disease but the long-term effects of untreated infection are still largely unknown. It has been suggested that these may include impairment of kidney growth, renal scarring, rise of blood pressure and kidney failure. Early diagnosis and treatment, therefore, offers the prospect of reducing mortality from kidney failure and of decreasing the workload of costly dialysis and transplantation centres.

In this monograph screening techniques for urinary tract infection are reviewed and the pathogenesis, natural history and response to treatment of these infections are discussed. With this as a basis, the value of screening healthy populations for urinary tract infections is assessed.

Screening Techniques

a) The concept of significant bacteriuria

Bacteriuria means the presence of bacteria in the urine. This may result from contamination during or after collection or it may indicate the presence of bacteria in the bladder urine. To distinguish amongst these possibilities, Kass[1] introduced the concept of significant bacteriuria. Human urine is an excellent medium for bacterial growth[2,3] and for this reason, bacteria can multiply rapidly in the bladder urine. Quantitative estimation of the bacteria in the urine, therefore, enables the distinction between contamination and infection. Organisms which have multiplied in the bladder urine before voiding will be present in large numbers (usually more than 100,000 organisms/ml of urine), whereas contaminants which are added to the urine during or after collection, are found in small numbers (usually less than 1000 organisms per ml of urine). The term significant bacteriuria applies to the presence of more than 100,000 organisms per ml of urine. When found in a single sample of urine which has been collected in the correct manner described below, it indicates with 90 per cent certainty that organisms are present in the bladder urine and that a second specimen would also yield a high count. If two consecutive urine samples reveal a bacterial count greater than 100,000 organisms per ml, this probability increases to

95 per cent[4]. The number of false positive results can be reduced even further if three consecutive samples of urine are examined. The realiability of this technique depends largely on the care taken over the collection of the urine. The number of false positive results will, therefore, vary from one centre to another and even within the same centre it will vary from one nurse who supervises the collection procedure to another. Since urinary tract infections are with few exceptions due to single bacterial strain, the specificity of the method can be enhanced by establishing serological identity of the organisms isolated from the two or more consecutive urine samples[5].

Significant bacteriuria is a statistical concept and it is not surprising, therefore, that in some instances bacteria are present in the bladder urine even though bacterial counts are less than 100,000 organisms per ml of urine. Such false negative results may be encountered under conditions of extreme diuresis when bladder emptying is frequent and insufficient time is available between successive acts of micturition for the bacteria in the bladder to attain a population density of 100,000 per ml of urine. A further reason why extreme diuresis may lead to false negative results is that the multiplication rate of pathogens in dilute urine is reduced[3]. Similarly when the urine is highly concentrated and acid bacterial multiplication may be reduced sufficiently to yield false negative results[3]. Also the presence of antibacterial agents in the urine leads to false negative results[1]. These exceptions do not detract from the value of quantitative bacteriological examination of the urine as a means of distinguishing infection from contamination without the need for catheterisation or suprapubic urine aspiration for it has been shown that human urine in the vast majority of an unselected population readily supports bacterial growth[3,6]. The demarcation between urinary infection and contamination at 100,000 organisms per ml of urine, therefore, holds true with few exceptions.

b) Collection of the urine specimens

In the diagnosis of significant bacteriuria, the technique of urine collection is critical. The technique used at the Boston City Hospital is both reliable and acceptable[4]. In the case of females the subject after washing her hands with soap is instructed by a trained nurse to wash the introitus from before backwards with each of four sterile gauze swabs that have been soaked in 10 per cent green soap solution. The subject is then taught to separate the labia with the fingers of one hand and to void directly into a sterile wide-mouthed container. The lid of the container is replaced by the nurse and the urine is then either cultured immediately or cooled to 4°C before culture to prevent multiplication of contaminants. There is no need for a mid-stream specimen and the whole procedure is best carried out with the subject straddling

over a lavatory basin. In the case of males, the glans penis is swabbed four times with green soap solution after drawing the prepuce back and a mid-stream specimen is collected. The type of cleansing agent is not critical although if powerful antiseptics are used, and these should inadvertently enter the collecting vessel, false negative results may be obtained[7].

In children urine collection presents a particularly difficult problem. Whereas the technique used in adults can readily be used for schoolchildren, these are not suitable for infants and neonates. A number of methods are available for such young children. A specially designed adhesive plastic bag may be used. Directly the infant has passed urine, the corner of the bag is cut off and the urine is allowed to run into a sterile container. Unfortunately, this technique produces a large number of false positive results. Virtanen *et al*[8] found that 16·5 per cent of positive results were due to contamination. Specially designed glass tubes[9] and Paul's tubing have been used but these methods suffere from the same disadvantage. The risk of obtaining urine specimens by catheterisation are well known[10] and this procedure should, therefore, be avoided. The best method of diagnosing urinary tract infection in the young subject is to obtain the urine by percutaneous suprapubic aspiration of the bladder[11]. This is facilitated by the intra-abdominal position of the bladder in this age group and apart from occasional slight haematuria the procedure has no complications in experienced hands[12]. This technique should be used when other attempts to establish the existence of urinary tract infection have left doubt. It has not so far been used as a screening technique amongst neonates and young children. Although such a study would be of great interest, it would not be justifiable on ethical grounds.

c) Transport of the urine specimens

Multiplication of contaminants in the urine after it has been voided must be prevented. If laboratory facilities are near to hand, this can be achieved by immediate culture of the urine. If not, the urine must be cooled to 4°C during transport. At this temperature multiplication of bacteria is prevented and few organisms die. Lower temperatures would result in a reduction of the viable count. Urine samples may be cooled by surrounding them with ice blocks in an insulated bag. Preservatives have been added to the urine to obviate the need for cooling. Addition of 1·8 per cent boric acid[13] prevents multiplication of bacteria without reducing colony counts. Another approach to the problem is the use of dip inoculum transport media which are inoculated on the spot and are then sent to the laboratory by post if necessary. Two such media exist, namely the Mackey and Sandys spoon[14,15] and the dip-slide devised by Gutmann and Naylor[16]. Finally, difficulties encountered in transporting urine specimens can of course be overcome by the use of a mobile laboratory.

d) Quantitative urine culture

The pour plate technique is the most accurate technique but it is demanding in time and materials. A simplified version of the technique has been introduced by the Boston City Hospital workers[4]. It requires only two petri dishes, one test tube containing 9·9 ml of broth and two sterile pipettes. Briefly 0·6 ml of urine is drawn up in the first pipette and 0·5 ml is placed in one of the petri dishes. The remaining 0·1 ml of urine is mixed with the 9·9 ml of broth. The contents of the tube are mixed and 0·1 ml of the 1 in 100 dilution of urine is placed in the second petri dish. The plates are poured at 45°C whilst the plate is moved gently in circular fashion to obtain mixing. After solidification, the plates are incubated overnight at 37°C. By inspection of the two plates it is possible to tell at a glance whether the urine contains more than 100,000 organisms/ml since up to 300 colonies can readily be counted on a plate. Thus 100 colonies or more on the plate containing 0·001 ml of urine indicates significant bacteriuria.

In the interest of speed and economy several semi-quantitative techniques have been introduced. These are acceptable provided their validity against the pour plate technique has been tested. The most commonly used semiquantitative method is to spread a standard bacteriological loopful of urine over the surface of a culture plate (surface viable counting). Brumfitt and Percival[17] introduced a filter paper strip technique. The strips are immersed in the urine and placed on McConkey agar plates. The advantage of this technique is that up to eight urine specimens can be tested in duplicate on a single plate. Both the dip-spoon and the dip-slide techniques overcome the problem of transporting urine samples whilst maintained at 4°C. The dip-slide has advantages over the spoon since the slide is coated with a selective medium on one side and nutrient agar on the other. Moreover, the surface area of the dip-slide far exceeds that of the spoon and it can therefore give a measure of the number of organisms present in the urine. Excellent correlations with the pour-plate method have been obtained[16,18] and initial reports on the use of dip-slides in population surveys are most encouraging[19]. The slides are now available commercially (Uricult supplied by Orion Ltd., Helsinki, Finland).

e) Microscopic examination of the urine

Microscopic examination of centrifuged or uncentrifuged urine is commonly used as an aid to the diagnosis of urinary tract infection. Particular emphasis is placed on the number of white cells and on the presence of bacteria. Pyuria, which is usually defined as more than five polymorphonuclear leucocytes per high power field is a particularly unreliable index of urinary tract infection. Only one third to one half of subjects with significant bacteriuria show pyuria[1]. Moreover, there are difficulties

in distinguishing white cells from renal tubular cells[20] and white cells are unstable in alkaline urine. Measurement of white cell excretion rate[21] with or without provocation by pyrogen[22] or steroids[23] is of little additional value in diagnosis.

In experienced hands, microscopic examination of Gram stained or unstained urine specimens for bacteriuria can give an 80 per cent correlation with the results of quantitative urine culture[1]. The method is fraught with dangers for the untrained observer. Firstly, it must be remembered the volume of urine which can be observed beneath a standard 22mm cover slip in one 'high-dry' field (magnification x 570) is of the order of $\frac{1}{80000}$ ml. At least 30,000 bacteria per ml of urine must be present before bacteria can be expected to be seen. Centrifugation of the urine as usually practised by clinicians who wish to preserve urinary casts, does not spin down bacteria. When gram negative rods are seen in centrifuged or uncentrifuged urine specimens, it is therefore, likely to be of significance provided that there are no vaginal epithelial cells in the urine since the microbial flora which adheres to these cells may give false positive results[24,25]. The untrained observer may further be confused by macromolecular aggregates of uromucoids which may resemble bacteria. This difficulty can be overcome by using gram stained preparations since uromucoids do not take up the stain. In summary, therefore, whereas pyuria has little value in screening for urinary tract infection, microscopic examination of gram stained urine smears is of considerable value in experienced hands. Furthermore, the number of false negatives and false positives can be reduced by examination of repeated urine specimens since the errors of the procedure occur in random fashion.

f) Chemical tests for bacteriuria

There is a need for a rapid and reliable test for bacteriuria akin to tests for albuminuria and glycosuria. Several such tests have been devised. Griess[26] considered that the presence of nitrites in the urine might indicate urinary tract infection since most enterobacteria reduce nitrates to nitrites. It was later shown[27] that such nitrites could be detected by a simple diazotisation reaction but when the test was applied to known infected urines it yielded positive results in only 60 per cent[28]. Despite close examination of the mechanism of nitrite formation by urinary pathogens[29] and the introduction of modifications of the original test such as addition of excess nitrate to the urine and prior incubation, the yield of positive tests remained in the region of 60 per cent of subjects with known infections of the urinary tract[30]. This may well be due to difficulties in standardisation of the test since urinary pathogens reduce nitrates to nitrites at varying rates and in some instances the reduction proceeds from nitrates through nitrites to ammonia leaving no nitrites to be detected in the urine. It should further be remembered that the performance of the Griess nitrite test or its modifications may not be without danger for technicians since the α naphthylamine

which is used for diazotisation of the nitrites has been cited as a cause of urinary tract tumours[31]. Another chemical test depends on the ability of respiring bacteria to reduce colourless tetrazolium salts to coloured formazans. Both triphenol tetrazolium chloride (TTC)[32] and alphanaphthyl tetrazolium[33] have been tested, and TTC seems to give the better results. Since the reduction of TTC by different bacterial species proceeds at a varying rate, it is, as in the case of the Griess test, difficult to standardise the test. When the test is standardised to detect 10^6 *Escherichia coli* per ml of urine, it fails to detect 10^7 *Pseudomonas aeruginosa*[4]. No matter how often the test is repeated, its sensitivity will not improve since errors of these chemical tests do not occur in a random manner. A further chemical test depends on the detection of urinary catalase[34]. The value of these three chemical screening tests has been compared with the results of quantitative urine culture in urines obtained from 3000 pregnant women[35]. The TTC test was found to detect significant bacteriuria in 86 per cent of the bacteriuric subjects, the nitrite test in 65 and the catalase test in 57 per cent. The TTC test is, therefore, the best of these chemical screening procedures but it is likely to miss important infections due to *Ps. aeruginosa*. The number of false negative results will depend on the kind of population under study. In domiciliary practice where most infections are due to coliform organisms few false negative results will be obtained whereas in hospital practice where relatively more infections are due to the less common urinary pathogens, the percentage of false negative results will be accordingly higher.

A recent novel approach to chemical screening for bacteriuria holds out greater promise than the tests discussed above. It is based on the observation that the glucose contained in normal urine (average 60 mg/L) is the major source of energy for the growth of urinary pathogens[36]. When organisms multiply in the urine, urinary glucose is reduced to subnormal levels (less than 10 mg/L). Schersten and Fritz[37] showed that in the fasting subject, these subnormal glucose levels indicated bacteriuria with great accuracy provided subjects with renal glycosuria and diabetes mellitus are excluded from consideration. The technique for detecting subnormal glucose levels in the urine can be automated and even a simple test paper technique has been devised for the detection of subnormal urinary glucose levels[38]. For this test the subject must be fasted overnight and a preservative should be added to the urine. The usefulness of preliminary screening for bacteriuria by this technique still needs further evaluation.

It must be born in mind that none of the chemical screening tests do away with the need for bacteriological examination of the urine but they enable these examinations to be confined to those subjects who give a positive result. It is the author's opinion that bacteriuria screening is best done by culturing the urine rather than by the indirect chemical tests here described.

Pathogenesis of Significant Bacteriuria

a) Source of urinary pathogens

Escherichia coli is by far the commonest urinary pathogen. It accounts for 80 to 90 per cent of infections seen in domiciliary practice. *E. Coli* has a complicated antigenic structure. Kauffmann[39] showed that it possesses somatic O antigen, flagellar H antigen and envelope K antigen. Specific antisera to these antigens can be prepared and by these means 149 O types, 90 K types and 49 H types of *E. Coli* have been identified. Infections of the urinary tract are usually due to a single strain. Serological identification of the strains responsible for urinary tract infections reveals that although many different strains can cause such infections, certain sero-types are more commonly isolated than others. The explanation for this observation may be that these common serotypes possess special pathogenicity for the urinary tract. An alternative and more likely explanation is that the strains of *E. coli* which are commonly involved in urinary tract infections merely reflect the prevalent faecal strains of the community from which the infected subjects are drawn. Numerous studies have been undertaken to distinguish amongst these alternatives[40-44]. Much of the confusion which surrounds the subject stems from the study of highly selected hospital populations. The carefully controlled studies of Grüneberg *et al*[44] which were undertaken in domiciliary practice clearly establish that there is close correspondence between the urinary and faecal strains of *E. coli* in subjects with urinary infection and that these urinary strains do not differ from those found in the faeces of non-infected controls drawn from the same domiciliary population. These findings suggest that strains of *E. coli* with special pathogenicity for the urinary tract do not exist and that the urinary pathogens encountered in domiciliary practice are derived from the prevalent faecal strains of the population. This is an important conclusion since it establishes that primary prevention of urinary tract infection cannot be achieved by eliminating pathogenic strains from the bowel since these pathogens are part of the population's normal bowel flora. Efforts to achieve primary prevention must, therefore, be directed to strengthening the defensive mechanisms of the urinary tract.

In hospital practice, the same considerations do not apply. In this environment infections may be transmitted directly to the urinary tract by instrumentation and the faecal flora may be changed by cross infection or therapy with antibacterial agents. The prevalence of urinary pathogens in such highly selected communities bears no relevance to the public health problem and will not be considered further except to point out that primary prevention of urinary infection can be achieved in the hospital by the avoidance of unnecessary instrumentation.

b) Mode of entry of pathogens into urinary tract

Most infections of the urinary tract arise by ascent of bowel organisms from the perineum, haematogenous infection being a rare occurrence. Stamey[45] has shown that in women with urinary tract infection, periurethral swabs frequently show a dense growth of organism identical to those isolated from the urine. The presence of faecal organisms on the perineal floor is encouraged by incontinence and the use of napkins in childhood[46] and poor hygienic habits in later life. The mechanism(s) whereby organisms on the perineal floor enter the bladder is not clear. Since the prevalence of urinary tract infection in females far exceeds that in males, it would seem reasonable to suggest that it is the shortness of the female urethra which facilitates entry of organisms but lack of prostatic secretions may also be relevant to this sex difference in incidence of urinary infection since prostatic fluid contains a bactericidal substance[47]. Sexual intercourse has been alleged to play an important role in the ascent of organisms from the perineum to the bladder. The prevalence of bacteriuria in the general female population is 12·8 times higher than in nuns of similar age[48]. Sexual contact might account for this difference but there are two observations which are at variance with this hypothesis. Firstly, bacteriuria is more common in young girls aged 6-18 than in young nuns[48]; secondly, it has been shown that the prevalence of bacteriuria in children rises steadily with age from five years onwards[49]. The effect of sexual intercourse has, therefore, been over emphasised even though it is common clinical experience that overt infection is precipitated by sexual contact, so-called 'honeymoon cystitis'. Other factors which may facilitate entry of faecal organisms into the bladder include retrograde flow through the urethra on bathing[50] and reversal of the peripheral part of the urinary stream as a result of turbulent flow through the female urethra[51].

If the 'dirty perineum' theory of the pathogenesis of urinary tract infection is correct, improvements in standards of personal hygiene could make an important contribution to the primary prevention of urinary tract infections. Some support for this view is forthcoming from the observation that the prevalence of bacteriuria is highest amongst the lower social classes[52,53].

c) Defensive mechanisms

Although human urine is an excellent medium for bacterial growth[3], organisms which enter the bladder do not invariably gain a foothold. The effectiveness of the defensive mechanisms of the bladder account for this. Two types of defensive mechanism have been described, namely hydrokinetic and mucosal[54]. The term hydrokinetic defence refers to the wash-out of bacteria by periodic voiding and

dilution by the inflow of urine from the kidneys. The size of the bacterial population attained by organisms which have entered the bladder urine depends on their growth rate in the urine, the urine flow rate, the size of the residual volume and the frequency of micturition. The relationship between these variables has been studied in mechanical[54] and computer[55] models and it has been shown that the clearance of organisms from the bladder in-vivo far exceeds that observed in the models[54]. This suggests that hydrokinetic defences alone cannot account for the rapid clearance of organisms from the normal urinary bladder.

The existence of a mucosal defence mechanism was demonstrated by Vivaldi *et al*[56]. They applied ^{32}P labelled *E. coli* directly to the exposed bladder mucosa of rabbits. By the end of one hour only 0·3 per cent of the inoculum had survived even though radio-activity in the mucosa persisted. It was suggested that a phagocytic mechanism accounted for this bactericidal effect of the intact bladder mucosa, the radio-active label remaining within the phagocytic cells after the organsisms had been killed. These results were confirmed by Norden *et al*[57] in guinea-pigs but it was shown that neither a phagocytic mechanism nor circulating antibodies accounted for the effect. It was postulated that organic acids produced by the mucosal cells might be responsible. Whatever the mechanism, it seems reasonable to suppose that the bactericidal properties of intact bladder mucosa limits the population size of invading pathogens and thus hastens their clearance by hydrokinetic defensive mechanisms. The balance between the bacterial multiplication rate and the effectiveness of the defensive mechanisms of the urinary tract determine whether or not infection is established after entry of pathogens into the urinary tract. Since the organisms which cause urinary tract infection do not possess special pathogenicity for the urinary tract, it seems likely that significant bacteriuria is due to a breakdown of the defensive mechanisms. In some instances, the cause of this breakdown is obvious, e.g. the neurogenic bladder or the existence of congenital anomalies which interfere with drainage. In other cases, the nature of the defect cannot be detected by existing methods. A profitable line for future research would be to study the defensive mechanisms of women liable to recurrent urinary tract infection since correction of defects of the defensive mechanisms would be preferable to the repeated or long-term use of antibacterial agents. The recent observations of Stamey *et al*[47] on the antibacterial action of prostatic fluid may provide a valuable clue. Is this factor missing in neonatal boys in whom the prevalence of urinary tract infection is higher than in neonatal girls? Does the female analogue of the prostate (the periurethral glands) produce a similar antibacterial agent and is it deficient in those women who are plagued by repeated infections of the urinary tract? The answers to these questions may have an important bearing on the prevention of urinary infection.

d) Renal involvement

The methods whereby bacteria once established in the bladder ascend to the kidney are incompletely understood. There seems little doubt that reflux of urine from the bladder to the kidney during micturition plays an important role. Although vesico-ureteric reflux was first described in 1903[58], interest in this subject has been revived only recently. Vesico-ureteric reflux does not occur in normal subjects[59] being prevented by the oblique course of the intramural portion of the ureter. Lich *et al*[60] who performed 3000 micturating cystograms, found that the abnormality was confined to children with urinary tract infection and Kunin *et al*[61] showed that the abnormality existed in 19 per cent of schoolgirls with asymptomatic significant bacteriuria. Similarly, Smellie[62] found reflux in 34 per cent of children with symptomatic infections of the urinary tract and she noted a close association between the presence of renal scars and reflux. In the absence of reflux, recurrent urinary tract infections seldom if ever cause renal scarring. There are three possible ways in which vesico-ureteric reflux may perpetuate infection and produce renal damage. Firstly, reflux provides a means of ascent of organisms to the kidney. Secondly it is a source of residual urine and thirdly it may produce damage by back pressure on the kidney. The relative importance of these effects is unknown. Equally, the mechanism whereby reflux is established is uncertain. It has been postulated[63,64] that amongst the many causes of reflux, e.g. congenital, traumatic and obstructive, bladder infection itself may produce vesico-ureteric reflux and thus facilitate renal infection.

It is clear from this brief account of the role of vesico-ureteric reflux in the pathogenesis of renal infection that screening for bacteriuria will reveal some subjects in whom infection is confined to the bladder and others in whom renal infection coexists. Thus Fairley *et al*[65] established by culture of ureteric urine specimens that 50 per cent of pregnant women with bacteriuria showed infection of the renal parenchyma. This distinction between bladder bacteriuria and renal bacteriuria is of utmost importance. To anticipate, it has been shown that acute symptomatic infections, radiological abnormalities of the kidney, defects of concentrating power and difficulties in treatment are more frequently encountered in subjects with renal bacteriuria than in those in whom the infection is confined to the bladder. Future studies of the natural history of significant bacteriuria must take the distinction between bladder and renal bacteriuria into account. It is not known to what extent bacteria which are initially confined to the bladder ascend to infect the renal parencyma. It may be that this progression occurs most frequently in childhood since bacteriuria in this age group is most commonly associated with vesico-ureteric reflux[61,62].

The diagnosis of renal involvement in bacteriuric subjects has been attempted by various means. Culture of renal biopsy specimens fails because of the patchy nature

of the inflammatory process[66]. The appearance in the urine of white cells with highly refractile cytoplasmic granules (so-called 'glitter' cells) is of limited value since white cells show the 'glitter' phenomenon whenever the urine is hypotonic[68]. The only reason why a correlation between the 'glitter' phenomenon and renal infection exists is that renal infection is frequently associated with a defect of renal concentrating power. Since there are many causes for urinary hypotonicity other than renal infection, this relatively simple test is of no real value in localising the site of infection. A direct approach to the localisation of infection in the urinary tract was adopted by Stamey *et al*[69]. It involves catheterisation of the ureters. With this technique it has been shown[65,70] that 50 per cent of pregnant women with bacteriuria show renal involvement. A simplified localisation technique which involves bladder catheterisation only has been devised[71] but it is clear that neither of these methods can be used in survey work.

Serum antibody levels to the O serotype of the infecting strain of *E. coli* have been shown to be a useful indirect method of diagnosing renal involvement[72]. A good correlation between raised antibody titres in excess of $\frac{1}{320}$ and renal infection has been observed[72] and it is clear that serum antibody level determination is the best method of localising infections of the urinary tract for survey purposes. In a series of 126 pregnant bacteriuric women[72], antibody titres were in excess of $\frac{1}{320}$ in 32 per cent. It would appear from this that estimation of serum antibody levels somewhat underestimates the frequency of renal involvement in pregnant women with bacteriuria.

Prevalence of Significant Bacteriuria

a) The neonate

There are no reliable data on the frequency of urinary tract infections in neonates because of the difficulties in obtaining uncontaminated urine samples. Lincoln and Winberg[73] using a careful cleaning technique, found that eight out of 298 boys had pronounced bacteriuria and pyuria whereas no evidence of infection was found amongst 286 girls. This predominance of urinary tract infections in males during the first few weeks of life has been noted by others[74,75,76] and is also reflected in post mortem studies[77]. It has been attributed to the greater frequency of congenital abnormalities of the urinary tract in males. After the first weeks of life, there is a marked excess of urinary tract infection amongst females which persists throughout childhood and adult life.

b) Schoolchildren

Kunin and his associates in the USA have studied the prevalence of bacteriuria in schoolchildren[61,78,79]. Amongst 16000 schoolgirls the prevalence was found to be 1·2 per cent as compared with 0·03 per cent amongst schoolboys. Two recent surveys in Britain[80,81] have confirmed Kunin's findings. More recently, it has been shown[49] that the prevalence of bacteriuria amongst schoolgirls rises steadily with age with an annual acquisition rate of 0·32 per cent. This is an important observation since it establishes that if bacteriuria screening should prove worthwhile as a preventive measure, it would have to be carried out repeatedly rather than be confined to one particular age group. This would add considerably to its cost and staff requirements.

c) Adults

The prevalence of bacteriuria has been studied amongst defined populations in South Wales[82], Jamaica[82] and Japan[83]. Although a detailed account of the studies in South Wales and Jamaica has not been published, it appears that the prevalence of bacteriuria amongst these strikingly different populations is remarkably similar. About 4 per cent of females between the ages of 16 and 65 show significant bacteriuria as compared with 0·5 per cent of males. Spontaneous remissions and new infections occur at the rate of about 1 per cent of the total female population per annum consequently at any given time the prevalence remains at about 4 per cent. In addition there is a turnover of bacteriuria within the population and the incidence of bacteriuria over a lifetime, therefore, far exceeds the prevalence. The exact incidence is still unknown but has been estimated at 10-20 per cent of the female population[82]. The prevalence of bacteriuria rises with age and also with parity but age is the more powerful factor. It appears to be less dependent on race and has not so far been shown to have a particular geographical distribution[84]. In pregnant women, bacteriuria does not appear to be more common than in the non-pregnant population but bacteriuria in pregnancy rarely remits spontaneously whereas in the non-pregnant adult spontaneous cure is a frequent occurrence[85,86].

Clinical Significance of Asymptomatic Significant Bacteriuria

Significant bacteriuria is an abnormal laboratory finding which indicates multiplication of bacteria in the bladder urine. Evaluation of its clinical significance requires descrip-

tion of the clinical, laboratory and radiological findings in bacteriuric and matched control populations together with a study of their subsequent fate. Few of the existing studies on the significance of bacteriuria satisfy these criteria and those that do mostly concern bacteriuria in pregnancy.

a) Clinical findings associated with significant bacteriuria

Bacteriuric populations differ in respect of their past medical history and blood pressure from non-infected control populations. Kunin and his colleagues noted that a previous history of urinary tract infection can be obtained from 28 per cent of bacteriuric schoolchildren as compared with 9·7 per cent of non-infected controls. Amongst adult bacteriuric women, 91 per cent give a past-history of symptoms possibly associated with urinary tract infection as compared with 62·5 per cent of matched controls. In 70 per cent of the bacteriuric subjects, symptoms occur during the year immediately preceding the detection of bacteriuria, whereas such a recent history of urinary infection is obtained from only 18 per cent of controls[85]. In adult males with bacteriuria a history of recent urinary tract instrumentation is usually obtained[82], whereas such a history is rarely given by bacteriuric women. These simple observations cast doubt on the use of the term asymptomatic bacteriuria but more importantly they show that in adults significant bacteriuria frequently fails to detect urinary tract infection at an early stage of its natural history. It might be argued that public awareness of the symptoms of urinary infection and of the need to report such symptoms would be almost as effective a way of early diagnosis as bacteriuria screening. It is not lack of symptoms but failure to report symptoms which makes bacteriuria 'asymptomatic'. It must be stressed that this argument does not apply to bacteriuria in childhood since the symptoms of urinary tract infection in this age group are usually vague.

Measurement of blood pressure in adult bacteriuric and matched control populations reveals that bacteriuric women have a somewhat higher blood pressure than do the controls[82,83,85,88]. It has been claimed[82] that bacteriuria may account for 10-20 per cent of hypertension in the general population. In pregnancy, an association between toxaemia and bacteriuria has been demonstrated by some workers[89,90,91] but denied by others[92,93,94]. The mechanism of the association between hypertension and urinary infection is obscure. Shapiro[95] suggested that hypertension sensitises the kidney to infection but this seems unlikely since hypertension is a familiar disorder whereas bacteriuria is not[82]. Eradication of bacteriuria does not lower blood pressure. This would suggest that the renal damage so frequently seen in bacteriuric individuals rather than the bacteriuria itself is responsible for the elevation of blood pressure.

b) Laboratory findings associated with significant bacteriuria

Adult bacteriuric women differ from matched controls in the following respects. Their mean erythrocyte sedimentation rate is marginally raised[85], their mean blood urea level is slightly elevated[85,91] and their renal concentrating power is impaired[96]. No difference in haemoglobin levels[85,97] or prevalence of persistent proteinuria[81,87] has been demonstrated. Since abnormalities of kidney function are the major concern of this monograph, these will be considered in a little more detail.

It has been recognised for some years[98] that patients with acute pyelonephritis fail to concentrate their urine maximally and that patients with so-called chronic pyelonephritis, may show a disproportionate decrease in concentrating power as compared with glomerular filtration rate[99]. Katz[96] demonstrated that in nine out of 20 pregnant women with asymptomatic bacteriuria, the urine could not be concentrated to more than 700 m. osmols/kg. This defect can be reversed by eradicating the bacteriuria[100]. This suggests that the defect in concentrating power is due to a reversible and perhaps biochemical lesion rather than the result of destruction of medullary tissue. Defects of renal concentrating power have been shown to correlate with elevation of serum antibody titres[101] and pregnant bacteriuric women who show the defect are much more likely to develop acute pyelonephritis than those who do not have this defect[102].

Blood urea levels have been studied in pregnant[91] and non-pregnant[85] women with bacteriuria. Blood urea levels were found to be marginally higher in the bacteriuric women than amongst matched controls. None of the bacteriuric women were found to have blood urea levels in excess of 55 mg per 100 ml. This seems surprising if bacteriuria is in fact an important cause of progressive kidney failure. There are no data on kidney function in children with 'asymptomatic' significant bacteriuria.

c) Radiological findings associated with significant bacteriuria

The radiological findings in schoolgirls and adults with bacteriuria have been well documented. In a series of 89 white schoolgirls, Kunin and Paquin[79] found abnormalities on excretion urograms in 22 per cent. These abnormalities included calicetasis in 16 per cent and reduplication in 4·5 per cent. Micturating cystograms revealed abnormalities in 43 per cent including vesico-ureteric reflux in 23 per cent, bladder trabeculation in 13·5 per cent and a large bladder in 11 per cent. Kincaid-Smith and Bullen[91] performed excretion urograms six weeks after delivery in 148 women found to have bacteriuria during pregnancy. Abnormalities were demonstrated in 51 per cent and acquired abnormalities (scars, stones, caliectasis, papillary necrosis and differences in kidney size) were found in 45 per cent of this series. Similar studies have been

carried out by Whalley *et al*[103], Gower *et al*[104] and Leigh *et al*[105] and these have yielded a lower prevalence of acquired renal disease, namely 20 per cent of the 131 subjects in Whalley's series, 21 per cent of the 71 subjects in Leigh's study and 14 per cent of the 163 women examined by Gower. The discrepancy between these findings and those of Kincaid-Smith and Bullen in Australia has been attributed to the widespread abuse of analgesics in that country. Abnormalities of the lower urinary tract in bacteriuric adults have been studied by Williams *et al*[106]. They showed vesico-ureteric reflux in 21 per cent of 100 bacteriuric adults who were found to have bacteriuria in pregnancy[9]. Bladder diverticula were found in 11 per cent. Although none of the foregoing studies have been controlled, it seems likely that significant bacteriuria delineates a population with a high prevalence of structural abnormalities of the urinary tract. This has been confirmed in a recent controlled study in which the prevalence of acquired renal abnormalities demonstrated by excretion urography was 18 per cent in adult non-pregnant bacteriuric women as compared with 6 per cent amongst matched non-infected controls[85].

d) Natural history of significant bacteriuria

Unless the natural history of untreated significant bacteriuria is known it is clearly impossible to assess the value of screening for significant bacteriuria. At present our knowledge of the natural history of significant bacteriuria is incomplete and what is known mostly concerns bacteriuria in pregnancy. This is but a small facet of the whole problem which requires long-term prospective studies of bacteriuric populations for its solution.

In pregnant women it has been shown that significant bacteriuria predisposes to the development of acute pyelonephritis. Some 20 per cent of pregnant bacteriuric women develop this complication and the risk can be largely avoided if the bacteriuria is eradicated by suitable treatment with antibacterial agents[107]. This relationship of bacteriuria in early pregnancy to acute pyelonephritis has received widespread confirmation although the reported incidence of acute pyelonephritis has varied between 14 and 63 per cent[108]. The prevention of acute pyelonephritis is one of the strongest arguments in favour of bacteriuria screening in pregnancy. It would clearly be an advantage if treatment of bacteriuria in pregnancy could be confined to the 20 per cent of pregnant bacteriuric women who go on to develop symptomatic infection. It has been shown that those women in whom renal infection exists as evidenced by raised serum antibody titres and defect of renal concentrating power are most likely to develop acute pyelonephritis later in pregnancy[102]. A case could, therefore, be made for refining bacteriuria screening in pregnancy by routine esti-

mation of serum antibody titres amongst bacteriuric women and confining treatment to those bacteriuric subjects in whom serum antibody levels are raised. The additional cost would be offset by a reduction of pharmaceutical expenditures and unnecessarily widespread use of antibacterial agents would be avoided.

Whereas the development of acute pyelonephritis in pregnant bacteriuric women is beyond question, claims[109] that pregnant bacteriuric women run a higher than expected risk of preeclamptic toxaemia, premature birth and foetal loss are more controversial. Even less certain is the suggestion[109] that eradication of the bacteriuria can reduce all these risks. Stuart *et al*[110] in Jamaica and Kincaid-Smith and Bullen[91] in Australia reported a significant increase in hypertensive disorders amongst pregnant women with bacteriuria but treatment did not diminish the incidence of toxaemia[91]. A large series of pregnant bacteriuric women studied by Little[92] in London, failed to show a relationship between bacteriuria and preeclamptic toxaemia. It is difficult to explain these divergent conclusions except on the basis of racial differences.

The association between maternal pyelonephritis and prematurity (birth weight less than 2·5 Kg) was first noted by Bredier in 1902[111] and has since been confirmed by others. Since bacteriuria in pregnant women predisposes to acute pyelonephritis, it might be expected that bacteriuria and prematurity are associated. Kass[112] reported that 24 per cent of pregnant bacteriuric women gave birth to premature babies and that eradication of the bacteriuria reduced the incidence to 10 per cent. Numerous studies have appeared since this report and these have been summarised by Whalley[108]. To-date, only five out of a total of 27 published studies have confirmed the existence of a significant relationship between bacteriuria and premature delivery. The design of some of these studies leaves much to be desired. In some studies[113,118], the diagnosis of significant bacteriuria was not well substantiated, in others[6,119] the diagnosis was made on the delivery table. Such a design misses out foetal losses which occur outside the hospital and includes women in whom bacteriuria was acquired late in pregnancy and in whom the bacteriuria could, therefore, have had little effect on the outcome of the pregnancy.

There are also a number of published studies[119,120] which showed suggestive trends but these did not reach statistical significance since the number of subjects studied was too small. In order to illustrate this point the results of 11 major studies were pooled by Beard and Roberts[121]. The mean incidence of prematurity amongst pregnant women with bacteriuria was 13·5 per cent as compared with 9·5 per cent amongst non-infected controls. Assuming a 5 per cent prevalence of bacteriuria amongst pregnant women, Beard and Roberts calculated that to show a significant difference at the 95 per cent level 6000 pregnant women would have to be screened and to show a difference at the 99 per cent level no less than 13000 pregnant women would have to be studied. A study of this scope has in fact been carried out recently

by Brumfitt and his colleagues in London[122]. 8907 pregnant women were screened for bacteriuria and a significant difference in mean birth weights of the babies of bacteriuric women (7lbs 3ozs) and those of non-infected controls (7lbs 6ozs) was found. The level of significance was $0{\cdot}05 > p > 0{\cdot}02$ corresponding to the theoretical calculations mentioned above. Brumfitt's study is of particular interest since it was shown that the risk of prematurity was highest amongst those women in whom bacteriuria was difficult to eradicate. Since difficulties in treatment appear to be correlated with the existence of structural abnormalities of the kidney (see below), this observation would suggest that it is the underlying renal damage rather than the bacteriuria itself which accounts for the association between premature delivery and bacteriuria. This would explain the failure of some investigators[91] to reduce the risk of prematurity by treatment of the bacteriuria. The link between prematurity and bacteriuria is further complicated by the role of socio-economic status, for mean birth weight is related to living standards. Since the prevalence of bacteriuria is also related to socio-economic class, it is difficult to eliminate this as the common factor responsible for both conditions.

The natural history of significant bacteriuria in non-pregnant women differs in two important respects from that of pregnant women. Firstly, there is a high spontaneous cure rate. Nearly 40 per cent of untreated bacteriuric women loose their bacteriuria over a period of one year[86]. These spontaneous cures are confined to those women in whom the urinary tract appears normal on excretion urography. The reason why such spontaneous remissions have not been recorded during pregnancy is unknown. It may be related to urinary stasis during pregnancy or to the constantly high urinary pH found in pregnant women which favours persistence of bacteriuria[3,123]. The second difference between the natural histories of bacteriuria in pregnant and non-pregnant women is that in the non-pregnant woman acute pyelonephritis rarely develops[86]. Amongst 92 non-pregnant bacteriuric women only two subjects developed loin pain with fever over a one year follow-up period, whereas symptoms of lower urinary tract infection (frequency and dysuria) developed in a further 30 of these women during this time. Furthermore the development of symptomatic infection was not prevented by a short course of treatment. In fact, this treatment encouraged the development of symptoms since the reinfections (i.e. infections with different organisms from those originally isolated) which followed initially successful treatment were more commonly associated with the development of symptoms than the persistent infections amongst untreated bacteriuric controls[86]. This would suggest that tolerance to the infecting strain of *E. coli* exists in the adult non-pregnant bacteriuric woman and that treatment disturbs this symbiosis. In this regard the demonstration by McCabe[124] that tolerance to the pyrogenic substances of gram negative bacteria exists in animals and humans with urinary tract infections is of particular interest.

The long-term effects of significant bacteriuria in adult women are still largely unknown. Freedman[125] and Andriole followed up 250 women with urinary tract infection for up to 12 years. Half of these patients had been followed for five or more years. No evidence of deterioration of kidney function or elevation of blood pressure has so far been observed. Our own experience which concerns 107 women with bacteriuria and extends over three years has been similar. There is, therefore, no evidence to suggest that untreated significant bacteriuria in the adult produces progressive kidney damage.

The sequelae of untreated infection in childhood may be more serious. Although controlled trials of the treatment of significant bacteriuria in childhood have not so far been published, there is evidence from the work of the University College Hospital Group that renal infection in childhood produces impairment of kidney growth and renal scars. Smellie and Normand[126] studied the progress of 369 children with urinary tract infection. Since most of these children were referred to them on account of symptoms albeit vague in many instances, all children had to be treated but in those children in whom infection was uncontrolled it was noted that kidney growth was impaired and renal scarring developed. These deleterious effects of kidney infection were confined to children in whom vesico-ureteric reflux existed. Eradication of the infection was found to restore kidney growth and prevent further scar formation. Since vesico-ureteric reflux is found in 19 per cent of schoolgirls with asymptomatic bacteriuria[61], it is possible that impairment of kidney growth and scar formation could be prevented by screening for bacteriuria and eradication of the infection. The growing kidney may be more susceptible to the damaging effects of infection than the adult kidney and some experimental evidence to confirm this has recently been obtained in this laboratory[127]. It is evident from the foregoing account that the most urgent need is for a controlled treatment trial of significant bacteriuria in childhood. Such studies are now in progress and an assessment of the value of bacteriuria screening in childhood must await their outcome.

Treatment of Significant Bacteriuria

Principles governing treatment rather than treatment regimes will be considered. Successful treatment requires adequate urinary concentration of an antibacterial agent to which the infecting organism is sensitive together with meticulous follow-up[69]. In domiciliary practice, initial treatment irrespective of the drug used or the duration of therapy, results in cure of bacteriuria in some 80 per cent of subjects[128]. In hospital practice a somewhat lower success rate is found. Unfortunately, these initial cures are

followed by recurrences. The introduction of sero-typing has facilitated a more detailed analysis of these recurrences. Reappearance of bacteriuria following treatment is of two distinct types with different temporal relationships and possibly different therapeutic implications. A recurrence of bacteriuria may either be due to *relapse*, i.e. infection with the same organism as that isolated before treatment or it may be due to *reinfection* with a different organism from that originally isolated. 88 per cent of relapses occur within the first month after treatment whereas the majority of reinfections occur from one to five months after treatment[129]. Whereas relapse usually indicates failure of treatment, reinfections indicate a defect of defensive mechanisms.

The frequency of recurrent infection following treatment is high. Little and de Wardener[130] showed that 76 per cent of subjects treated for acute pyelonephritis developed a recurrence of infection within 18 months. This experience has been shared by others[104,105]. In our own series[86] of non-pregnant women with asymptomatic bacteria, infection recurred in 45 per cent over a follow-up period of one year. Even in children with significant bacteriuria, Kunin *et al*[87] found that 75 per cent of infections which were cured initially, recurred within two years. The duration of the initial therapy appears to have no influence on the recurrence rate[128,131]. This would argue against the use of extended courses of treatment. Furthermore, Grüneberg *et al*[122] pointed out that short-term treatment of bacteriuria in pregnancy is preferable since it facilitates the recognition of those women in whom reinfections are common and in whom the highest incidence of acute pyelonephritis and premature delivery is found.

From this brief consideration of the difficulties in treating bacteriuria, it emerges that if bacteriuria screening is to be introduced as a service procedure, adequate provisions for follow-up of bacteriuric subjects must be made since treatment in many instances results in a temporary rather than lasting cure.

The Rationale of Screening for Bacteriuria

There is no doubt that urinary tract infection is an important public health problem. A survey conducted by the General Register Office and the College of General Practitioners[132] revealed that the consultation rate for urinary tract infection is 11 per 1000 consultations. Moreover, mortality statistics reveal an increase in deaths from infections of the kidney which may not be entirely due to a change in diagnostic habit and acuity[133,134].

The diagnosis of urinary tract infection in a latent phase of the disease is now possible by methods acceptable to the population at reasonable cost. Brumfitt and Reeves[135] estimated that the cost of screening for bacteriuria amounted to less than five shillings per person. Facilities for screening would be relatively simple to provide in antenatal clinics but if bacteriuria screening were to be extended to schoolgirls and non-pregnant adult women, the provision of facilities and staff would involve a considerable expenditure.

The value of screening for significant bacteriuria in pregnancy is well established since treatment of the bacteriuria largely prevents maternal pyelonephritis. In 1965, there were 874,000 births in England and Wales. The cost of bacteriuria screening would, therefore, amount to approximately £218,000 at five shillings per screening test. If 8 per cent of these women were found to have one positive culture, the cost of repeat cultures would amount to approximately £17,500. If significant bacteriuria were confirmed in 5 per cent of the women (43,700) and each of these were given a one week course of a sulphonamide costing five shillings, the cost of treatment would amount to £11,000. The total annual expenditure on antenatal screening and treatment would, therefore, be of the order of £250,000. This must be set against the reduction of expenditure on hospital admission for acute pyelonephritis[136]. Acute pyelonephritis would be prevented in 20 per cent of the 43,700 bacteriuric women, i.e. 8,740 women. It is not known by how many of these women require hospital admission but it has been suggested[136] that half of them would occupy a hospital bed for two weeks at £50 per week. This amounts to a saving of approximately £440,000. Bacteriuria screening in pregnancy as part of routine antenatal care is, therefore, a sound proposition both on medical and economic grounds.

The above conclusion does not apply to the vast majority of bacteriuric women, i.e. those who are not pregnant. Treatment of bacteriuria by means suitable for large scale use confers no benefit on them. Screening of adult, non-pregnant women could only be justified if long-term prospective studies should show that bacteriuria produces progressive kidney damage leading to kidney failure which can be prevented by treatment. So far, the results of such studies do not show such a trend and it seems unlikely that bacteriuria screening amongst non-pregnant adult women will make an important contribution to preventive medicine.

The most urgent need is for studies of the long-term sequelae of bacteriuria in childhood. Evidence that the growing kidney is more susceptible to damage resulting from infection than the adult kidney is already forthcoming. It is important, therefore, that controlled trials of treatment of asymptomatic bacteriuria in childhood are performed to evaluate the benefits while they are still in doubt.

1 Kass, E. H. (1956). *Asymptomatic infections of the urinary tract. Trans. Assn. Amer. Phsns.* **69,** 56.

2 Pasteur, L. (1863). *Examen du rôle attribué au gaz oxygene atmospherique dans la destruction des matières animales et végétales après la mort. Compt. Rend. Acad. Sci.* (Paris) **56,** 734.

3 Asscher, A. W., Sussman, M., Waters, W. E., Davis, R. H. and Chick, S. (1966). *Urine as a medium for bacterial growth. Lancet* **2,** 1037.

4 Norden, C. W. and Kass, E. H. (1968). *Bacteriuria of pregnancy – A critical appraisal. Ann. Rev. Med.* **19,** 431.

5 Kunin, C. M. (1966). *Asymptomatic bacteriuria. Ann. Rev. Med.* **17,** 383.

6 Waters, W. E., Sussman, M. and Asscher, A. W. (1967). *A community study of urinary pH and osmolality. Brit. J. Prev. Med.* **21,** 129.

7 Roberts, A. P., Robinson, R. E. and Beard, R. W. (1967). *Some factors affecting bacterial colony counts in urinary infection. Brit. med. J.* **1,** 400.

8 Virtanen, S., Okanen, T. and Peltonen, T. (1962). *Colony counts and the diagnosis of urinary tract infection in infants and children. Ann. Paediat. Fenn.* **8,** 269.

9 Houston, I. B. (1963). *Pus cells and bacterial counts in the diagnosis of urinary tract infection in childhood. Arch. Dis. Childh.* **38,** 600.

10 Beeson, P. B. (1958). *The case against the catheter. Amer. J. Med.* **24,** 1.

11 Pryles, C. V., Atkin, M. D., Morse, T. S. and Welch, K. J. (1959). *Comparative bacteriological study of urine obtained from children by percutaneous suprapubic aspiration of the bladder and by catheter. Paediatrics* **24,** 983.

12 Ekyn, S. and Newman, C. G. H. (1969). *Suprapubic puncture. Brit. J. Hosp. Med.* **2,** 863.

13 Porter, I. A. and Brodie, J. (1969). *Boric acid preservation of urine samples. Brit. med. J.* **1,** 353.

14 Mackey, J. P. and Sandys, G. H. (1965). *Laboratory diagnosis of infections of the urinary tract in general practice by means of a dip-inoculum transport medium. Brit. med. J.* **2,** 1286.

15 Mackey, J. P. and Sandys, G. H. (1966). *Diagnosis of urinary infections. Brit. med. J.* **1,** 1173 (c).

16 Guttmann, D. E. and Naylor, G. R. E. (1967). *Dip-slide: An aid to quantitative urine culture in general practice. Brit. med. J.* **3,** 343.

17 Brumfitt, W. and Percival, A. (1964). *Pathogenesis and laboratory diagnosis of non-tuberculous urinary tract infection.* A review. *J. Clin. Path.* **17,** 482.

18 Cohen, S. and Kass, E. H. (1967). *A simple method for quantitative urine culture. New eng. J. Med.* **277,** 176.

19 Lohi, S. and Thysell, H. (1969). *Screening for bacteriuria by mail. in Abstr. 4th Int. Congr. Nephrol.* Stockholm Vol. **1** p. 382.

20 Prescott, L. F. and Brodie, D. E. (1964). *A simple differential stain for urinary sediment. Lancet* **2,** 940.

21 Hutt, M. S. R., Chambers, J. A., McDonald, S. J. and de Wardener, H. E. (1961). *Pyelonephritis. Observations on the relation between various diagnostic procedures. Lancet* **1,** 351.

22 Leather, H. M., Wills, M. R. and Gault, H. M. (1963). *Bacterial pyrogen in diagnosis of pyelonephritis. Brit. med. J.* **1,** 92.

23 Little, P. J. and de Wardener, H. E. (1962). *The use of prednisone phosphate in the diagnosis of pyelonephritis in man. Lancet* **1,** 1145.

24 Sandford, J. P., Favour, C. B., Mao, F. H. and Harrison, J. H. (1956). *Evaluation of positive urine culture; approach to differentiation of significant bacteriuria from contaminants. Amer. J. Med.* **20,** 88.

25 Kunin, C. M. (1961). *The quantitative significance of bacteria visualised in the unstained urinary sediment. New eng. J. Med.* **265,** 589.

26 Griess, P. (1879). *Bemerkung zur Abhandlung der H. H. Weselsky und Benedickt: 'Uber enige Azoverbindungen'. Ber. Deut. Chem. Ges.* **12,** 426.

27 Cruickshank, J. and Moyes, J. M. (1914). *The presence and significance of nitrites in the urine. Brit. med. J.* **2,** 712.

28 Beechgaard, P. and Jansen, K. F. (1943). *Nitritreaktion ved urnvevsinfektion. Nord. Med. T.* **20,** 2134.

29 Kahler, R. L. and Guze, L. B. (1957). *Evaluation of the Griess nitrite test as a method for the recognition of urinary tract infection. J. Lab. clin. Med.* **49,** 934.

30 Smith, L. G., Thayer, W. R., Malta, E. M. and Utz, J. P. (1961). *Relationship of the Griess nitrite test to bacterial culture in the diagnosis of urinary infection. Ann. int. Med.* **54,** 66.

31 Simons, L. A. and Williams, J. D. (1967). *Alpha Naphthylamine test for bacteriuria. Lancet* **1,** 442 (c).

32 Simons, L. A. and Williams, J. D. (1962). *A simple test for significant bacteriuria. Lancet* **1,** 1377.

33 Smith, L. G. and Schmidt, J. (1962). *Evaluation of three screening tests for patients with significant bacteriuria. J. Amer. Med. Assn.* **181,** 431.

34 Braude, A. L. and Berkovitz, H. J. (1961). *Detection of urinary catalase by disk flotation. J. Lab. clin. Med.* **57,** 490.

35 Kincaid-Smith, P., Bullen, M., Mills, J., Fussell, U., Huston, N. and Goon F. (1964). *The reliability of screening tests for bacteriuria in pregnancy. Lancet* **2,** 6.

36 Weiser, R., Asscher, A. W. and Sussman, M. (1969). *Glycosuria and the growth of urinary pathogens. Invest. Urol.* **6,** 650.

37 Schersten, B. and Fritz, H. (1967). *Subnormal levels of glucose in urine: a sign of urinary tract infection. J. Amer. Med. Assn.* **201,** 949.

38 Scherstén, B., Dahlovist, A., Fritz, H., Kohoer, L. and Westlund, L. (1968). *Screening for bacteriuria with a test paper for glucose. J. Amer. Med. Assn.* **204,** 205.

39 Kauffmann, F. (1944). *Zur Serologie der Coli-Gruppe. Acta path. microbiol. Scand.* **21,** 20.

40 Vahlne, G. (1945). *Serological typing of the colon bacilli, with special reference to the occurrence of B. col. inman in normal and pathological conditions, particularly in appendicitis. Acta. path. microbiol. Scand. Suppl.* **62,** 1.

41 Rantz, L. A. (1962). *Serological grouping of Esch. coli: Study in urinary tract infection. Arch. intern. Med.* **109,** 37.

42 Turck, M. and Petersdorf, R. G. (1962). *The epidemiology of non-enteric Esch. coli infections: prevalence of serologic groups. J. Clin. Invest.* **41,** 1760.

43 Vosti, K. L., Goldberg, L. M., Monto, A. S. and Rantz, L. A. (1964). *Host-parasite interaction in patients with infections due to Esch. Coli. 1. Sero-grouping of Esch. coli from intestinal and extra-intestinal sources. J. clin. Invest.* **43,** 2377.

44 Grüneberg, R. N., Leigh, D. A. and Brumfitt, W. (1968). *E. coli serotypes in urinary tract infection: Studies in domiciliary, antenatal and hospital practice. in Urinary tract Infection.* ed. F. O'Grady and W. Brumfitt, Oxford University Press p. 68.

45 Stamey, T. A. (1968) personal communication.

46 Smallpiece, V. (1966). *Urinary infection in the two sexes. Problems of aetiology. Lancet* **2,** 1019.

47 Stamey, T. A., Fair, W. R., Timothy, M. M. and Chung, H. K. (1968). *Antibacterial nature of prostatic fluid. Nature Lond.* **218,** 1444.

48 Kunin, C. M., McCormack, R. C. (1969). *An epidemiologic study of bacteriuria and blood pressure among nuns and working women. New eng. J. Med.* **278,** 635.

49 Kunin, C. M. (1968). *Emergence of bacteriuria, proteinuria and symptomatic urinary tract infections among schoolgirls followed for seven years. Pediatrics* **41,** 968.

50 Mitchie, A. J. (1959). *Paediatric urology. Summary of a round table. Pediatrics* **24,** 1118.

51 Hinman, F. Jr. (1966). *Mechanisms for the entry of bacteria and the establishment of urinary infection in female children. J. Urol.* **96,** 546.

52 Henderson, M., Entwistle, G., Tayback, M. (1962). *Bacteriuria and pregnancy outcome: preliminary findings. Amer. J. Publ. Health* **52,** 1887.

53 Turck, M., Goffe, B., Petersdorf, R. G. (1962). *Bacteriuria of pregnancy. Relation to socio-economic factors. New eng. J. Med.* **266,** 857.

54 Cox, C. E. and Hinman, F. Jr. (1965). *Factors in resistance to infection of the bladder. In Progress in pyelonephritis.* ed. E. H. Kass and F. A. Davis, Philadelphia. p. 53.

55 O'Grady, F., Gauci, C. L., Watson, B. W. and Hammond, B. (1968). *In-vitro models stimulating conditions of bacterial growth in the urinary tract. In Urinary Tract Infection* ed. F. O'Grady and W. Brumfitt, Oxford University Press p. 80.

56 Vivaldi, E., Munõz, J., Cotran, R. and Kass, E. H. (1965). *Factors affecting the clearance of bacteria within the urinary tract in Progress in pyelonephritis.* ed. E. H. Kass and F. A. Davis, Philadelphia p. 531.

57 Norden, C. W., Green, G. M. and Kass, E. H. (1968). *Antibacterial mechanisms of the urinary bladder. J. clin. Invest.* **47,** 2689.

58 Sampson, J. A. (1903). *Ascending renal infection with special reference to the reflux of urine from the bladder into the ureters as an aetiological factor in its causation and maintenance. Bull. John Hopkins Hosp.* **14,** 334.

59 Jones, B. W. and Headstream, J. W. (1958). *Vesico-ureteral reflux in children. J. Urol.* **80,** 114.

60 Lich, R., Howerton, L. W., Goode, L. S. and Davis, L. A. (1964). *The uretero-vesical junction of the newborn. J. Urol.* **92,** 436.

61 Kunin, C. M., Southall, I. and Paquin, A. J. (1960). *Epidemiology of urinary tract infections. A pilot study of 3057 school children. New eng. J. Med.* **263,** 817.

62 Smellie, J. M. (1967). *Medical aspects of urinary infection in children. J. Roy. Coll. Physns. Lond.* **1,** 189.

63 Rosenheim, M. L. (1965). *Vesico-ureteric reflux in Progress in Pyelonephritis.* ed. E. H. Kass and F. A. Davis, Philadelphia p. 599.

64 Garrett, R. A., Rhamy, R. K. and Carr, J. R. (1961). *Non-obstructive vesico-ureteral regurgitation. Trans. amer. Assn. Genitourin. Surg.* **53,** 120.

65 Fairley, K. F. and Bond, A. G. (1966). *The site of infection in pregnancy bacteriuria. In Abstr. of III Int. Congr. Nephrol.* Washington D.C. Vol. **2** p. 188.

66 Kipnis, G. P., Jackson, G. G., Dallenbach, F. D. and Schoenberger, J. A. (1955). *Renal biopsy in pyelenephritis. Arch. Int. Med.* **95,** 445.

67 Sternheimer, R. and Malbin, B. (1951). *Clinical recognition of pyelonephritis with a new stain for urinary sediments. Amer. J. Med.* **11,** 312-323.

68 Poirier, K. P. and Jackson, G. G. (1957). *Characteristics of leukocytes in the urine sediment in pyelonephritis. Amer. J. Med.* **23,** 579.

69 Stamey, T. A., Govan, D. E. and Palmer, J. M. (1965). *The localisation and treatment of urinary tract infections: the role of bactericidal urine levels as opposed to serum levels. Medicine* (Baltimore) **44,** 1.

70 Fairley, K. F., Bond, A. G., Adey, F. D., Habersberger, P. and McCredie, M. (1966). *The site of infection in pregnancy bacteriuria. Lancet* **1,** 939.

71 Fairley, K. F., Bond, A. G., Brown, R. B. and Habersberger, P. (1967). *Simple test to determine the site of urinary tract infection. Lancet* **2,** 427.

72 Percival, A., Brumfitt, W. and de Louvois, J. (1964). *Serum antibody levels as an indication of clinically inapparent pyelonephritis. Lancet* **2,** 1027.

73 Lincoln, K. and Winberg, J. (1964). *Studies of urinary tract infections in infancy and childhood. II Quantitative estimation of bacteriuria in unselected neonates with special reference to the occurrence of asymptomatic infections. Acta Paediat.* **53,** 307-316.

74 Craig, W. S. (1935). *Urinary disorders occurring in the neonatal period. Arch. Dis. Childh.* **10,** 337.

75 Miller, J. F. (1937). *Pyuria in the newborn. Ohio St. med. J.* **33,** 621.

76 Stansfield, J. M. (1966). *Clinical observations relating to the incidence and aetiology of urinary tract infections in children. Brit. med. J.* **1,** 631.

77 Neumann, C. G. and Pryles, C. V. (1962). *Pyelonephritis in infants and children. Amer. J. Dis. Childh.* **104,** 215.

78 Kunin, C. M., Zacha, E. and Paquin, A. J. (1962). *Urinary tract infections in school-children. L. Prevalence of bacteriuria and associated urological findings. New. Eng. J. med.* **266,** 1287.

79 Kunin, C. M. and Paquin, A. J. (1965). *Frequency and natural history of urinary tract infection in schoolchildren in Progress in Pyelonephritis.* ed. E. H. Kass and F. A. Davis, Philadelphia p. 33.

80 Savage, D. C. L., Wilson, M. I., Ross, E. M. and Fee, W. M. (1969). *Asymptomatic bacteriuria in girl entrants to Dundee primary schools. Brit. med. J.* **3,** 75.

81 Meadow, R. S., White, R. H. R. and Johnston, N. M. (1969). *Prevalence of symptomless urinary tract disease in Birmingham schoolchildren. I Pyuroa and Bacteriuria. Brit. med. J.* **3,** 81.

82 Kass, E. H., Savage, W. and Santamarina, B. A. G. (1965). *The significance of bacteriuria in preventive medicine. In Progress in pyelonephritis.* ed. E. H. Kass and F. A. Davis, Philadelphia p. 3.

83 Freedman, L. R., Phair, J. P., Seki, M., Hamilton, H. B., Nefzger, M. D. and Hirata, M. (1965). *The epidemiology of urinary tract infections in Hiroshima. Yale J. Biol. Med.* **37,** 262.

84 Kass, E. H. (1966). *Geographic pathology of bacteriuria. In The Kidney. International Academy of pathology monograph No. 6.* Williams and Wilkins, Baltimore p. 469.

85 Sussman, M., Asscher, A. W., Waters, W. E., Evans, J. A. S., Campbell, H., Evans, K. T. and Williams, J. E. (1969). *Asymptomatic significant bacteriuria in the non-pregnant woman. 1. Description of Population. Brit. Med. J.* **1,** 799.

86 Asscher, A. W., Sussman, M., Waters, W. E., Evans, J. A. S., Campbell, H., Evans, K. T. and Williams, J. E. (1969). *Asymptomatic significant bacteriuria in the non-pregnant woman. LL Response to treatment and follow-up. Brit. med. J.* **1,** 804.

87 Kunin, C. M., Deutscher, R. and Paquin, A. (1964). *Urinary tract infection in school-children: an epidemiological, clinical and laboratory study. Medicine* **43,** 91.

88 Miall, W. E., Kass, E. H., Ling, J. and Stuart, K. L. (1962). *Factors influencing arterial pressure in the general population in Jamaica. Brit. med. J.* **2,** 497.

89 Norden, C. W. and Kilpatrick, W. H. (1965). *Bacteriuria of pregnancy in Progress in Pyelonephritis.* ed. E. H. Kass and F. A. Davis, Philadelphia p. 64.

90 Stuart, K. L., Cummins, G. T. M. and Chin, W. A. (1965). *Bacteriuria, prematurity and the hypertensive disorders of pregnancy. Brit. med. J.* **1,** 554.

91 Kincaid-Smith, P. and Bullen, M. (1965). *Bacteriuria in pregnancy. Lancet* **1,** 395.

92 Little, P. (1966). *The incidence of urinary infection in 5000 pregnant women. Lancet* **2,** 925.

93 Bryant, R. E., Windom, R. E., Vineyard, J. P. Jr. and Sandford, J. P. (1964). *Asymptomatic bacteriuria in pregnancy and its association with prematurity. J. Lab. Clin. Med.* **63,** 224.

94 Monzon, O. T., Armstrong, D., Pion, R. J., Deigh, R. and Hewitt, W. L. (1963). *Bacteriuria during pregnancy. Amer. J. Obstet. Gynaecol.* **85,** 511.

95 Shapiro, A. P. (1963). *Experimental pyelonephritis and hypertension. Implications for the clinical problem. Ann. Int. Med.* **59,** 37.

96 Kaitz, A. L. (1961). *Urinary concentrating ability in pregnant women with asymptomatic bacteriuria. J. clin. Invest.* **40,** 1331.

97 Kaitz, A. L. and Hodder, E. W. (1961). *Bacteriuria and pyelonephritis of pregnancy. A prospective study of 616 pregnant women. New eng. J. Med.* **265,** 667.

98 Winberg, J. (1958). *Renal concentration capacity during acute non-obstructive urinary tract infections in infancy and early childhood. Acta. Paediat.* **47,** 635.

99 Brod, J. (1956). *Chronic pyelonephritis. Lancet* **2,** 973.

100 Norden, C. W. and Tuttle, E. P. (1965). *Impairment of urinary concentrating ability in pregnant women with asymptomatic bacteriuria in Progress in Pyelonephritis.* ed. E. H. Kass and F. A. Davis, Philadelphia p. 73.

101 Reeves, D. S. and Brumfitt, W. (1968). *Localisation of urinary tract infection. In Urinary tract infection.* ed. F. O'Grady and W. Brumfitt, Oxford University Press p. 53.

102 Elder, H. A. and Kass, E. H. (1965). *Renal function in bacteriuria of pregnancy. In progress in pyelonephritis.* ed. E. H. Kass and F. A. Davis, Philadelphia p. 81.

103 Whalley, P. J., Martin, F. G. and Peters, P. C. (1965). *Significance of asymptomatic bacteriuria detected during pregnancy. J. amer. Med. Assn.* **193,** 879.

104 Gower, P. E., Haswell, B., Sidaway, M. E. and de Wardener, H. E. (1968). *Follow-up of 164 patients with bacteriuria of pregnancy. Lancet* **1,** 990.

105 Leigh, D. A., Grüneberg, R. N. and Brumfitt, W. (1968). *Long-term follow-up of bacteriuria in pregnancy. Lancet* **1,** 603.

106 Williams, G. L., Davies, D. K. L., Evans, K. T. and Williams, J. E. (1968). *Vesico-ureteric reflux in patients with bacteriuria in pregnancy. Lancet* **2,** 1202.

107 Kass, E. H. (1960). *The role of asymptomatic bacteriuria in the pathogenesis of pyelonephritis. In Biology of pyelonephritis.*

108 Whalley, P. J. (1967). *Bacteriuria of pregnancy. Amer. J. Obstet. Gynec.* **97,** 723.

109 Kass, E. H. (1960). *Bacteriuria and pyelonephritis of pregnancy. Arch. Int. Med.* **105,** 194.

110 Stuart, K. L., Cummins, G. T. M. and Chin, W. A. (1965). *Bacteriuria, preeclamptic toxaemia and prematurity in Progress in pyelonephritis.* ed. E. H. Kass and F. A. Davis, Philadelphia p. 45.

111 Bredier, F. (1902). *L'étude de certaines formes de pyelonephritis au cours de la grossesse* (Thesis de Paris).

112 Kassm, E. H. (1960). *Hormones and host resistance to infection. Bact. Rev.* **24,** 177.

113 Dixon, H. G. and Brant, H. A. (1967). *Significance of bacteriuria in pregnancy. Lancet* **1,** 19.

114 Layton, R. (1964). *Infection of the urinary tract in pregnancy: An investigation of a new routine in antenatal care. J. Obstet. Gynec.* **71,** 927.

115 Pinkerton, J. H. M., Houston, J. K. and Gibson, G. L. (1965). *Significant bacteriuria during pregnancy. Proc. Roy. Soc. Med.* **58,** 1041.

116 Hipple, R. F. and Schulman, H. (1965). *Bacteriuria in pregnancy. Obstet. Gynecol.* **26,** 396.

117 Low, J. A., Johnston, E. E., McBride, R. L. and Tuffnell, P. G. (1964). *The significance of asymptomatic bacteriuria in the normal obstetric patient. Am. J. Obstet. Gynecol.* **90,** 897.

118 Sleigh, J. D., Robertson, J. G., Isdale, M. H. (1964). *Asymptomatic bacteriuria in pregnancy. J. Obstet. Gynecol.* **71,** 74.

119 Turck, M., Goffe, B. and Petersdorf, R. G. (1962). *Bacteriuria of pregnancy. New eng. J. Med.* **266,** 857.

120 Constable, P. (1966). *The triphenyl tetrazolium chloride test in general practitioner antenatal care. Lancet* **2,** 195.

121 Beard, R. W. and Roberts, A. P. (1968). *Asymptomatic bacteriuria during pregnancy. Brit. med. Bull.* **24,** 44.

122 Grüneberg, R. N., Leigh, D. A. and Brumfitt, W. (1969). *Relationship of bacteriuria in pregnancy to acute pyelonephritis, prematurity and foetal mortality. Lancet* **2,** 1.

123 Asscher, A. W., Sussman, M. and Weiser, R. (1968). *Bacterial growth in human urine in urinary tract infection.* ed. F. O'Grady and W. Brumfitt, Oxford University Press p. 3.

124 McCabe, W. R. (1963). *Endoloxin tolerance.* 11. *Its occurrence in patients with pyelonephritis. J. clin. Invest.* **42,** 618.

125 Freedman, L. R. and Andriole, V. T. (1969). *A long-term study of women with urinary tract infections. in Abstr. IV Int. Congr. Nephrol.* Stockholm. Vol. **1** p. 386.

126 Smellie, J. M. and Normand, I. C. S. (1968). *Experience of follow-up of children with urinary tract infection. In Urinary tract infection.* ed. F. O'Grady and W. Brumfitt, Oxford University Press p. 123.

127 Asscher, A. W. and Chick, S. (1970). *The effect of ascending* E. coli *infection on compensatory hypertrophy of the rat kidney* – in preparation.

128 Williams, J. D., Reeves, D. S., Condie, A. P., Franklin, I. S. N., Leigh, D. A. and Brumfitt, W. (1968). *The treatment of bacteriuria in pregnancy in Urinary tract infection.* ed. F. O'Grady and W. Brumfitt, Oxford University Press p. 160.

129 McCabe, W. R. and Jackson, G. G. (1965). *Evaluation of factors influencing therapeutic response in chronic pyelonephritis. In progress in pyelonephritis.* ed. E. H. Kass and F. A. Davis, Philadelphia p. 728.

130 Little, P. J. and de Wardener, H. E. (1966). *Acute pyelonephritis incidence of reinfection in 100 patients. Lancet* **2,** 1277.

131 Gower, P. E. (1968). *Long-term therapy in chronic renal infections. In Urinary tract infection.* ed. F. O'Grady and W. Brumfitt, Oxford University Press p. 235.

132 Logan, W. P. D. and Cushion, A. A. (1958). *Morbidity Studies from General Practice: Studies on Medical and Population Subjects No. 14:* HMSO.

133 Kessner, D. M. and Florey, C. V. (1967). *Mortality trends for acute and chronic nephritis and infections of the kidney. Lancet* **2,** 979.

134 Waters, W. E. (1968). *Trends in mortality from nephritis and infections of the kidney England and Wales. Lancet* **1,** 241.

135 Brumfitt, W. and Reeves, D. S. (1968). *Screening procedures for urinary infection in Presymptomatic detection and early diagnosis.* ed. C. L. E. H. Sharpstone and H. Keen, Pitman Medical, London p. 179.

136 Wilson, J. M. G. (1968). *Bacteriuria in pregnancy in screening in medical care.* Nuffield Provincial Hospital Trust p. 15.

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