often when antibacterial treatment was successful than in patients where urinary infection persisted. Unfortunately, it was not always possible to decide whether the improvement of the anaemia resulted from the elimination of infection or from more intensive iron therapy.

While the significance of iron deficiency in these cases remained obscure, there was little evidence to suggest that folic-acid deficiency played a relevant part in the causation of their anaemia. This might have been anticipated, as most of them were on a prophylactic regimen which includes folic acid. Although pregnant women are often reluctant to take iron, few default on their folic acid.

Only 16 patients presented with the clinical signs and symptoms of pyelitis or cystitis. In 82% the infection was quite symptomless. Routine laboratory investigation of the urine in pregnancy would therefore appear to be advisable, especially at the beginning of the third trimester. Many cases of urinary infection in pregnancy are undoubtedly missed or erroneously diagnosed as "albuminuria," as a result of simple side-room testing. Urinary infection should be suspected in all cases of anaemia which have not responded to routine iron and folic-acid therapy, and once diagnosed should be treated promptly and energetically.

Summary

The incidence of urinary infection has been determined in 463 cases of anaemia in pregnancy; they were compared with 447 normal pregnant women. The great majority of patients and controls had been receiving routine prophylactic iron and folic acid.

Urinary infection was more than twice as common in the anaemic patients as in the controls. In 30 out of 56 cases the infection cleared on antibacterial drug therapy and in most of these the anaemia also responded.

Evidence of iron deficiency was present in more than half of the anaemias with urinary infection, but folic-acid deficiency appeared to be uncommon in these cases.

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PREVENTION OF CATHETER INFECTION OF URINE IN FEMALE PATIENTS

BY

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Open drainage of the male or female bladder by indwelling catheter is very apt to cause urinary infection. Intermittent catheterization carries a smaller but still appreciable risk. Even the simple passage of a sterile catheter may introduce organisms from the introitus or urethra into the bladder. Kass (1957) reported an infection rate of 2-4% after a single catheterization. Slade and Linton (1960) reported an infection rate of 29% in obstetric patients who were catheterized once for therapeutic reasons. Brumfitt *et al.* (1961) also found a high infection rate (22.8%) in obstetric patients who required therapeutic catheterization because of complicated or difficult labour, but a lower rate (9.1%) in patients who were catheterized solely to obtain urine for examination. The risk of infection is increased with repeated catheterization or with an abnormal urinary tract. The danger of catheter-induced infection should be avoided by using mid-stream specimens of urine when possible instead of catheter specimens for diagnostic purposes in female patients as well as males (*British Medical Journal*, 1961). When catheterization is essential the risk of infection should be reduced by employing a correct aseptic technique. In this paper we report trials of two methods of further reducing the risk by the prophylactic use of disinfectants. In one method the urethra was disinfected before passing the catheter. In the other the bladder was disinfected after catheterization.

The laboratory methods and the criteria for the diagnosis of infection were described by Gillespie *et al.* (1960) and by Slade and Linton (1960).

Disinfection of the Urethra

This procedure was studied in gynaecological patients who were catheterized intermittently after operation. The patients were admitted, without selection, to two adjacent wards (D and F), which were administered as one by the same nursing staff. The number of catheterizations per patient, which varied from 5 to 59 (average 22), was almost identical in the two wards.

Two disinfectants were studied: (a) hydrargaphen ("penotrane") urethral jelly, which contained phenylmercuric dinaphthylmethane disulphonate (0.05%) and a local anaesthetic, and (b) chlorhexidine digluconate ("hibitane") 0.5% in a mixture of polyethylene glycols

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which was viscid at room temperature but fluid at body temperature (G. H. Darling, personal communication). Later in the investigation mercuric oxycyanide 1 in 2,000 was incorporated in the chlorhexidine cream.

The disinfectant preparations were supplied in plastic urethral syringes (see Fig.) manufactured by the Flexile Metal Co. Each syringe was used several times, but a separate one was kept for every patient.

Plastic urethral syringe.

The urethras of patients in ward F were disinfected before and during operation and before every subsequent catheterization. After cleansing the vulva with sterile saline, the nozzle of the syringe, lubricated by expressing a little of its contents, was fully inserted into the urethra and then withdrawn while 0.5–1 ml. was injected. The catheter was passed after at least three minutes (during which time the nurse washed her hands and prepared a catheter tray).

In the control ward (D) the technique of catheterization was the same as in ward F except that disinfectants were not used. Because of the difficulty of maintaining sterility a non-disinfectant cream was not instilled into the urethra. Instead, catheters were lubricated with sterile "K-Y" jelly.

A mid-stream specimen of urine and a urethral swab were obtained within 24 hours of admission. Catheter specimens were taken at operation and daily thereafter for as long as the patient was catheterized. All urines were cultured, and most were examined microscopically. During the trial of the chlorhexidine cream, urine specimens from treated and control patients were collected in amounts of approximately 20 ml. in sterile bottles with 2 ml. of broth containing "lubrol W" (5%) and lecithin (2.5%). This was shown to neutralize chlorhexidine in a concentration of 1 in 2,500.

Results

Of 217 patients admitted, 15 (7%) already had infected urine and were excluded from the trial; 22 who were given antibiotics or sulphonamide before the onset of infection, and 9 who were treated with indwelling catheters, were also excluded. The 171 patients who remained in the trial had the following operations: anterior colporrhaphy in 29, posterior colporrhaphy in 7, anterior and posterior colporrhaphy in 26, "Manchester repair" in 45, and vaginal hysterectomy and repair in 64.

The incidence of urinary infection is shown in Table I. Of 16 patients who were treated with hydrargaphen, 8 (50%) became infected by Gram-negative bacilli, a result no better than in the simultaneous control group of 14 patients. Of 59 patients who were treated with chlorhexidine, 11 (17%) became infected by Gram-negative bacilli, compared with 27 (52%) of the 52

control patients. This difference was statistically significant ($\chi^2=12.2$; $P<0.01$). An attempt was then made to improve the results by incorporating mercuric oxycyanide 1 in 2,000 in the chlorhexidine cream, since previous work (Linton, 1958) had shown that the action of chlorhexidine on bacteria *in vitro* could be enhanced in this way; but the results were no better than with chlorhexidine alone (Table I).

The value of chlorhexidine was also demonstrated by a calculation which showed that the incidence of bacillary infection in the chlorhexidine-treated group was 1 per 93 catheterizations (1.1%) compared with 1 per 34 catheterizations (2.9%) in the control group. In the hydrargaphen-treated group the incidence was 1 per 20 catheterizations.

Most of the bacilli which caused infection were lactose-fermenting coliform strains. The proportion of infections by *Pseudomonas* and *Proteus* species did not increase significantly when chlorhexidine cream was used. Of the Gram-negative bacilli isolated from the urine of chlorhexidine-treated patients, six were coliforms, one was *Pseudomonas*, and four were *Proteus* sp., compared with 17 coliforms and 10 *Proteus* sp. in the corresponding control group. But the success of chlorhexidine in preventing bacillary infections did not

TABLE I.—Effect of Disinfecting the Urethra on the Incidence of Urinary Infection in Catheterized Patients

Urethral Treatment and Date	Treated Groups			Control Groups		
	No. of Patients	Infections by		No. of Patients	Infections by	
		Gram-neg. Bacilli	<i>Str. faecalis</i>		Gram-neg. Bacilli	<i>Str. faecalis</i>
Hydrargaphen June–August, 1960	16	8 (50%)	3 (19%)	14	7 (50%)	5 (36%)
Chlorhexidine March–May, 1960	11	1	2	11	7	1
September, 1960–June, 1961	48	10	13	41	20	10
Total	59	11 (17%)	15 (25%)	52	27 (52%)	11 (21%)
Chlorhexidine + mercuric oxycyanide July–October, 1961	19	3 (16%)	4 (21%)	11	5 (45%)	5 (45%)

extend to *Streptococcus faecalis*. Streptococcal infections were not reduced at all even when the period of contact with chlorhexidine cream prior to catheterization was prolonged to five minutes. The failure was probably due to the relative insensitivity of *Str. faecalis* to chlorhexidine. This was demonstrated *in vitro* by adding one drop of overnight broth culture to an aqueous solution of chlorhexidine 0.02%, held at room temperature, and subculturing loopfuls at intervals to lecithin–lubrol W agar. A strain of *Escherichia coli* was sterilized in less than half a minute, compared with three minutes with *Str. faecalis*.

Fortunately, streptococcal infections were less severe than bacillary infections. Table II shows the incidence of pyuria (more than 15 leucocytes per high-power field of centrifuged deposit) starting within three days of the commencement of infection by different organisms.

TABLE II.—Pyuria in Relation to Infecting Organisms

Infecting Organism	No. of Patients*	No. with Pyuria
None	61	0
<i>Str. faecalis</i> (alone)	48	2 (4%)
Gram-negative bacilli	48	39 (81%)

* Some were included more than once (see text).

Some patients who left hospital less than three days after the onset of infection had to be omitted from this comparison; a few others who successively developed infections at intervals of at least three days were included more than once. Only 4% of infections by *Str. faecalis* caused pyuria, compared with 81% of infections by Gram-negative bacilli. Hence, although the protection afforded by chlorhexidine was incomplete, severe infections were usually prevented (Table III).

TABLE III.—Incidence of Pyuria in Relation to Method of Disinfecting Urethra

Disinfectant	No. of Patients	No. with Pyuria
None	57	22 (39%)
Hydrargaphen	10	5 (50%)
Chlorhexidine	72	11 (15%)

The value of disinfecting the urethra was also demonstrated by comparing organisms isolated from the urethra on admission to hospital with those which subsequently caused infection. Gram-negative bacilli were isolated from the urethral swabs of seven control patients, four of whom subsequently developed urinary infections by similar organisms and two more by different organisms. Swabs from seven subsequently treated patients also contained Gram-negative bacilli, but none developed urinary infections by the same organisms (although three patients became infected by different organisms).

Disinfection of the Bladder After Catheterization

This procedure was investigated in obstetric patients who were admitted to wards A and B for delivery at term and who were catheterized once. (In accordance with our routine practice, catheterization was performed only when required for therapeutic reasons.) The disinfectant procedure, which was originally employed by Paterson *et al.* (1960) in gynaecological patients, consisted in instilling 2 oz. (57 ml.) of an aqueous solution of chlorhexidine digluconate 1 in 5,000 into the bladder before the catheter was removed. In this concentration chlorhexidine did not irritate the bladder when used as an irrigating fluid by Beeuwkes and de Vries (1956).

Mid-stream specimens of urine were obtained on admission, and again on the second or third day after delivery. If a post-partum specimen was found to be infected the result was confirmed by examining another specimen two days later. Catheter specimens when obtained were also examined.

Of the 480 patients admitted 43 (9%) were excluded from the investigation because their urine was already infected on admission. This incidence was similar to that found in our gynaecological patients, reported above, and accords well with the incidence found by other workers (Kass, 1956, 1960; Lytton, 1961). Seventeen patients who were catheterized more than once were also excluded. Of the remaining 420 patients, 272 were catheterized once; and the effect of chlorhexidine treatment was investigated in them. Ninety-one patients, mostly in the catheterized group, were given antibiotics or sulphonamide, and their results were recorded separately.

After an initial control period all patients who were catheterized in ward A were treated with chlorhexidine, while those in ward B served as controls. Later the procedure was reversed between the wards.

Results

The results were similar in the two wards and are summarized in Table IV. In the patients who were not given antibiotics or sulphonamides, the incidence of infection was only 1.5% among those who were not catheterized, compared with 28% of those who were catheterized without chlorhexidine treatment. It must be remembered that the liability to infection of the catheterized patients was probably increased by the circumstances which made catheterization necessary. The protective action of chlorhexidine was strikingly

TABLE IV.—Incidence of Urinary Infection After a Single Catheterization During Labour. Effect of Instilling Chlorhexidine Solution into the Bladder

Treatment Group	Antibiotics and Sulphonamide	
	Not Given (Infections/ Total Patients)	Given (Infections/ Total Patients)
Not catheterized	2/145 (1.5%)	0/3
Catheterized, without chlorhexidine	36/129 (28%)	6/61 (10%)
Catheterized, with chlorhexidine	3/55 (5.5%)	0/27

shown by the much lower incidence of infection (5.5%) in the catheterized patients who were treated with it. The difference was highly significant ($\chi^2 = 10.3$; $P < 0.01$).

The protective action of chlorhexidine was also apparent in the patients who received antibiotics and sulphonamides (Table IV).

It was interesting to observe that infections by *Str. faecalis* were reduced as much as Gram-negative bacillary infections. The difference between this success and the failure of urethral disinfection to control streptococci was probably due to the more prolonged contact between the disinfectant solution and the organisms in the bladder.

Discussion

The true incidence of infection after catheterization can only be determined by systematic bacteriological study, since the symptoms are sometimes slight. Our results, and those of several other workers, show that infection is in fact very common, especially when there is interference with the normal functioning of the lower urinary tract. At the same time the seriousness of the infections should not be exaggerated. A follow-up study of some of our patients (unpublished) showed that many infections cleared up spontaneously or with simple treatment, and Kaye *et al.* (1962) came to the same conclusion. However, catheter-induced infections are so common that much ill-health is caused by the minority which become chronic or recurrent. There can therefore be no disputing the oft-repeated advice that unnecessary catheterization should be avoided.

When catheterization is necessary—and it often is—it should be performed aseptically, by trained persons, using a correct type of catheter (Slade and Linton, 1960). The risk of infection can be further reduced by local antisepsis. Both of the methods which we studied were of value; but they cannot be directly compared, since the patients in whom they were investigated were probably dissimilar in their liability to infection. However, consideration of our results in conjunction with those published by Paterson *et al.* (1960) suggests that disinfection of the bladder gives more protection than disinfection of the urethra. On the other hand, it

may not always be desirable to instil fluid into the bladder. If chlorhexidine solution is instilled its concentration should not exceed 1/5,000, since there is some evidence that stronger solutions—for example, 1/1,000—may irritate the bladder mucosa (Paterson *et al.*, 1960). Both procedures should therefore be of practical value and preferable to the prophylactic administration of systemic antibiotics, which is likely to breed drug-resistant pathogens.

Summary

Two methods of preventing urinary infection after catheterization of female patients have been investigated. Disinfection of the urethra prior to catheterization, by means of a lubricant containing chlorhexidine, was moderately effective against Gram-negative bacilli but not against *Streptococcus faecalis*. The instillation of chlorhexidine solution into the bladder after catheterization was very effective against all species of organisms encountered.

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INCIDENCE OF MALFORMATIONS SINCE THE INTRODUCTION OF THALIDOMIDE

BY

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Material

Several recent reports indicate that administration of thalidomide ("distaval") in early pregnancy may be followed by the birth of a malformed child. Most of the affected children have had reduction deformities of the limbs, sometimes associated with malformations of the ears, eyes, or viscera (McBride, 1961; Burley, 1962; Ferguson, 1962; Lenz, 1962a, 1962b; Morgan, 1962; Pfeiffer and Kosenow, 1962a, 1962b; Rogerson, 1962; Russell and McKichan, 1962; Stabler, 1962; Willman and Dumoulin, 1962). These defects have become much commoner since the introduction of thalidomide (Lenz, 1961; Wiedemann, 1961; Pfeiffer and Kosenow, 1962a, 1962b; Watson, Slater, and McDonald, 1962), and the combined results of five inquiries in the United Kingdom and Germany show that the drug was taken during pregnancy by mothers of at least 55 of 71 affected children (Lenz, 1961; Devitt and Kenny, 1962; Dunn, Fisher, and Kohler, 1962; Jones and Williamson, 1962; Speirs, 1962). Experimental evidence is also available: if pregnant rabbits are given a large dose of thalidomide similar malformations occur in a high proportion of the offspring (Somers, 1962).

The observations so far reported have been obtained by *ad hoc* inquiry, and it has not been possible to assess in a defined population of births either (a) the extent of the increase in frequency of reduction deformities of the limbs, or (b) whether the incidence of other malformations has also increased. In the present communication we attempt to provide this information using data for all Birmingham births in the five years 1957–61. This period was chosen because thalidomide was first marketed in the United Kingdom in April, 1958, and used increasingly during the next three years. As a result the risks of exposure to thalidomide in early intrauterine life were practically non-existent for children born in 1957–8, but increased steadily thereafter.

Data were recorded for two groups of children born in 1957–61: those who were stillborn or who died before the end of 1961 while resident in Birmingham, and those living in Birmingham at the end of 1961. Our sources of information about stillbirths and dead children were: (1) the records kept by the Public Health Department, including information obtained from birth histories, death certificates, and necropsy reports; and (2) the original necropsy reports of a few children whose other records were insufficiently precise. Details of survivors were obtained by requesting all health visitors in the city to furnish particulars of living malformed children on their lists.

A comparison with earlier results (McKeown and Record, 1960) suggests that there was reasonably complete ascertainment of all serious external malformations except cleft lip and palate. This deficiency was corrected by scrutinizing lists of patients treated for cleft lip and palate in local hospitals.

Reduction Deformities of Limbs

Table I shows the number of reduction deformities of the limbs that occurred in each year. There were four instances of sirenomelia (fusion of the lower limbs). This defect is quite different from the others in appearance, and has not become commoner. Eleven children had reduction deformities of the thumbs or radii. These defects often occur together (Potter, 1952), and as they are sometimes associated with thrombocytopenia and Fanconi's anaemia (Nilsson and Lundholm, 1960) they are regarded as aetiologically distinct from the other reduction deformities listed, which do not exhibit these associations. Seven of the 11 instances of radial and thumb defects occurred in 1958. A fuller account of them will appear elsewhere (Leck and Millar, 1962).