

devised, but the introduction of the new urine-bag is believed to have been an important factor in the marked fall of the infection rate during the last year. This bag has also been found very effective in preventing urinary infection in patients having abdomino-perineal excisions of rectum or other operations when periods of continuous urine drainage of up to one week are necessary. We are also using it to collect the bile drained through a T-tube after exploration of the common bile-duct.

Bladder wash-outs are well known to involve risk of introducing infection. While they were found necessary in most of the early cases, the introduction of mannitol made it possible to discontinue them. It is impossible to obtain perfect haemostasis after prostatectomy. There is always some oozing blood in the immediate post-operative period, but this will stop spontaneously in a few hours if haemostasis is adequate. The good flow of urine obtained with an infusion of mannitol has prevented the formation of clots and obstruction of the catheter, making wash-outs unnecessary. We have found that the six hours following the operation are the most critical in this respect and have limited the administration of mannitol to this period, though it could be continued longer if necessary.

Mannitol, an osmotic diuretic, overcomes the physiological post-operative antidiuresis. It is being extensively used for prevention of acute renal failure after certain surgical operations, but this is a rare complication of prostatectomy. As pointed out above, we use it mainly to obtain a good flow of urine, which will prevent clots blocking the catheter. To avoid water-depletion a fluid load of about 1,000 ml. is given during the operation.

Intravenous urea has been used with a similar purpose (McKelvie, 1962). We felt reluctant to administer urea in case of obstruction of the urinary tract. From experimental evidence Bounous *et al.* (1960) concluded that "it might be considered unwise to utilize urea in patients who have marginal or reduced renal function." Comparative studies by Rabelo *et al.* (1962) have shown mannitol to be preferable to urea as an osmotic diuretic.

Some form of antibacterial "cover" was given to all patients in the series while the catheter was *in situ*. It certainly did not prevent infection during the first part of the series, and it is doubtful whether it had any influence on the infection rate during the second part. I have in the past seen two cases of fatal bacteraemic shock due to superinfection by resistant micro-organisms while the patients were on broad-spectrum antibiotics.

Summary

The high incidence of urinary infection after prostatectomy, especially by *Ps. pyocyanea*, was markedly reduced by the adoption of three measures: immediate or early prostatectomy whenever possible, the introduction of a new closed system of drainage, and the use of the osmotic diuretic mannitol in the immediate post-operative period.

I wish to thank Mr. E. B. Z. Masterman, under whose care the patients were admitted, for allowing me to treat them and for his encouragement. I am also grateful to the laboratory, radiological department, operating-theatre, and nursing staff for their help and co-operation.

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Value of Prophylactic Antibacterial Therapy in Instrumentation of Urinary Tract

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In the practice of urology instrumentation of the urinary tract is necessary in both diagnosis and treatment. That this carries a risk of infection is well documented, but the evidence as to the extent of this risk, and to whether it can be reduced by prophylactic antibacterial therapy, is scanty and to some extent contradictory. For this reason it was decided to carry out a controlled trial with an antibiotic given before instrumentation of the urinary tract. The antibiotic chosen was demethylchlortetracycline (Ledermycin), which, like the other tetracyclines, is absorbed rapidly from the gastro-intestinal tract, has a wide spectrum of antibacterial activity, is excreted in the urine, and has few side-effects. Demethylchlortetracycline is excreted more slowly than the other tetracyclines, thus maintaining an adequate serum and urine level for up to 48 hours after a single oral dose.

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Material and Methods

Most of the patients who took part in this survey were attending the urological clinic of the London Hospital; a few were in-patients. Patients who agreed to take part in the survey were instructed to provide a midstream specimen of urine, the specimen being collected in a glass jar after careful cleansing of the genitalia with cetrimide. In order to avoid a bias in either the test or control groups towards more or less extensive procedures the patients were allocated into categories depending on the anticipated type of instrumentation.

Appropriate information about the patient was recorded on standard forms so that it could later be coded and analysed on punched cards. The forms for consecutive patients in each category were numbered consecutively, and the treatment for each patient was provided in four red capsules enclosed in an envelope attached to the form, so that no confusion in

administration was likely to occur. Some treatments contained demethylchlortetracycline (150 mg. per capsule, total dose 600 mg.), and an approximately equal number contained no active drug but were not visibly different. The code by which treatments could be identified was held in the department of pharmacology. No member of the surgical or nursing staff knew which treatments were active, and no untoward effects occurred during the trial, so that it was not necessary to break the code.

The patients then waited for at least an hour, after which the appropriate instrumental manoeuvre was carried out. A note was made on the data sheet as to the type of instrumentation which had been performed, and also an indication of its duration and as to whether haematuria resulted. A minority of these procedures were performed under general anaesthesia. Among conscious patients no local anaesthetic was used in females, and Lidothesein (lignocaine HCl B.P. 1% and chlorhexidine gluconate solution 0.25% in a lubricant base) was used in the males. Urethral sounds and cystoscope sheaths were sterilized by boiling for five minutes before use. Cystoscope telescopes were sterilized by immersion in chlorhexidine solution 1:2,500 for at least five minutes. The external urinary meatus was cleaned with 1:5,000 solution of chlorhexidine or with cetrimide 1%, depending on the type of instrumentation. Where needed, irrigation was performed with 1:5,000 chlorhexidine. The instruments were lubricated with K.Y. gel.

The patient was seen again three or four days later and questioned regarding the presence of symptoms, their time of onset in relation to the instrumentation, and their duration. A midstream specimen of urine was taken. All urine samples were placed in a refrigerator within 15 minutes of collection and conveyed to the laboratory within two hours, where they were again refrigerated. A standard loop with an internal diameter of 3 mm. was inserted into the urine and removed vertically. The urine was then plated on to a blood agar and a MacConkey plate, following the same pattern of plating on each occasion. The plates were incubated at 37° C. for 24 hours and colony counts were performed. A similar method was described by Cattell and Lefford (1963), and the results were found to correlate well with those obtained by the pour plate technique.

The bacterial count (in organisms per ml.) was then calculated, and for the purposes of this survey a count of greater than 10,000 per ml. was regarded as indicative of infection (Efferse and Jensen, 1963). In most cases the count was not repeated, but where the second (post-instrumentation) count was either higher or lower than the first (pre-instrumentation) count at least one further sample was obtained and cultured. White cell counts were performed by centrifuging approximately 10 ml. of urine for five minutes. The supernatant was poured off and the deposit examined, counting the number of white cells per high-power field.

Results

The number of instrumental procedures that were performed was 212 (Table I). Most of these patients had been subjected to instrumentation or to operations involving the presence of

TABLE I.—Instrumental Procedures in Control and Test Group

Instrumental Procedures	Control Group (105)			Test Group (107)		
	Males	Females	Percentage of Total	Males	Females	Percentage of Total
Anterior dilatation ..	15	—	14.3	9	—	8.4
Posterior ..	32	—	30.5	21	—	19.6
Cystoscopy ..	29	13	40	41	17	54.2
Closed cystodiathermy	11	1	11.4	14	—	13.1
Retrograde pyelogram or ureterogram ..	2	2	3.8	3	2	4.7
	89	16		88	19	

indwelling catheters previously, but in 20% an instrument was passed along the urethra for the first time.

Patients were regarded as having acquired infection if their urine contained fewer than 10,000 organisms per ml. before instrumentation, and more than this number after instrumentation (Table II). Five of the six patients in this category were

TABLE II.—Cases Apparently Infected at Instrumentation

Code No.	Diagnosis	Instrumentation	Bacterial Count	Symptoms	White Count (Cells/H.P.F.)		Organisms
					Before	After	
C91	Recurrent papilloma	Cystoscopy	100,000	None	> 5	> 5	<i>Str. faecalis</i>
D11	Carcinoma of bladder	Closed cystodiathermy	100,000	"	< 5	> 5	<i>E. coli</i>
D12	"	"	100,000	Frequency and pain	< 5	> 5	" "
D22	Recurrent papilloma	Cystoscopy	10,000	Frequency	> 5	> 5	" "
D33	Anterior stricture	Anterior dilatation	10,000	None	< 5	< 5	<i>Proteus</i>
A35	"	"	10,000	Frequency	< 5	> 5	<i>E. coli</i>

in the treated group, only one in the control group. At least two further samples of urine have been obtained from each of these patients, and, with one exception, have been found to be sterile. No antibiotic treatment other than the dose of demethylchlortetracycline is known to have been given to any of these patients. The exception, a patient who has been attending at frequent intervals during the last 10 years for fulguration of recurrent vesical papillomata, has a persistent *Escherichia coli* bacilluria which has so far resisted attempts at elimination. However, *Esch. coli* had been cultured from this patient's urine on several previous occasions, so that it is unlikely that the infection was acquired at this occasion.

In 10 patients bacterial counts of greater than 10,000 at the first visit had been reduced below this figure on the second occasion. Six of these patients were treated, four were controls. Four of the six treated patients had suffered a recent attack of overt infection of the urinary tract, which was thought to have subsided on clinical grounds but which was still active on the evidence of bacilluria. It is probable that these four patients benefited from the administration of an antibiotic, since a further colony count again showed a level of less than 10,000 organisms per ml.

Ten patients complained of symptoms suggestive of infection of the urinary tract after instrumentation, but no organisms were cultured from the urine either before or after instrumentation. Six of these patients were treated, four were controls.

Sixteen patients were found to have counts of 10,000 organisms per ml. before instrumentation, and a similar level afterwards. Seven of these patients were treated, nine were controls. An analysis of this group and of the other patients presenting with bacilluria is seen in Table III.

TABLE III.—Analysis of Cases Found to Have Bacteriuria* at First Visit

Lesion	No. of Patients	Remarks
Bladder neoplasm needing repeated cystoscopy	8	5 had undergone previous open operation
Posterior stricture ..	10	3 had had a suprapubic cystostomy in the past
Anterior stricture (following prostatectomy)	5	1 was in the treated category and reverted to sterile after instrumentation
Recent attack of cystitis ..	3	All in treated category, all reverted to sterile

* Organisms grown: *Esch. coli* (10), *Proteus* (8), *Klebsiella pneumoniae* (3), *Staph. saprophyticus* (2), *Pseudomonas pyocyanea* (2), *Str. faecalis* (1).

Discussion

There is little doubt that organisms which are potentially pathogenic exist in the distal urethra (Helmholz, 1950), and that these organisms can be transferred to an instrument intro-

duced into the urethra (Guze and Beeson, 1956). On the other hand, the normal bladder shows considerable resistance to infection when bacteria are introduced (Cox and Hinman, 1961), and Clarke and Joress (1960) have demonstrated spontaneous disappearance of bacteria from the urine after operation involving the use of an indwelling catheter.

Reference to Table IV will show the incidence of bacteriuria which has been found by various authors to develop after instrumentation of the urinary tract. It will be seen clearly

TABLE IV.—Incidence of Bacteriuria Found by Various Authors After Instrumentation of Urinary Tract

Source	Category of Patient	Type of Instrumentation	Significant Level of Bacteriuria (Organisms/ml.)	% Infected
Marple (1941)	Female in-patients	Instrumentation or catheterization	100,000	5% (of 100)
Kass (1957)	Male and female patients	Single catheterization	100,000	2% (of 350)
Jackson and Griebel (1957)	"	Repeated catheterization	100,000	3% (of 58 patients, 169 procedures)
Davis <i>et al.</i> (1959)	Obstetric patients	Single catheterization	10,000	29% (of 221)
Slade and Linton (1960)	"	1. Single catheterization	10,000	22% (of 77)
		2. No instrument passed	10,000	3% (of 72)
Brumfit, Davies, and Rosser (1961)	"	1. Catheterized for specimen	100,000	9.1% (of 110)
		2. Catheterized for obstetric reasons—e.g., retention, forceps delivery, etc.	100,000	22.8% (of 105)
		3. Not catheterized	100,000	4.7% (of 105)
Lytton (1961)	Male urological patients	Cystoscopy	Routine culture	1.8% (of 110)
Rehm (1962) (control group)	Urological patients	"	100,000	2.2% (of 97)
Turck and Petersdorf (1962)	Ambulatory males and females	Single catheterization	100,000	1% (of 100)
Present series: (control group)	Urology patients	Various types of instrumentation	10,000	1% (of 105)

that there are two sharply contrasting categories of patient, and that the rate of infection among obstetric patients is very much higher than among those patients in whom instruments are passed for other reasons. Indeed, the occurrence of spontaneous bacteriuria (at 3% to 4.7%) unrelated to instrumentation is higher in obstetric patients than in other groups who actually undergo instrumentation. The infection rates appear to be remarkably constant at about 20% to 30% in obstetric patients and 1% to 3% in other categories. As against this, however, the patients who are found to have bacilluria frequently have a past history of instrumentation, and it seems reasonable to ascribe a cause-and-effect relationship. Grossberg *et al.* (1962) studied 230 patients in whom infection of the urinary tract was present. They found that in 59% the infection appeared to be "hospital acquired," and in most of these the infection followed instrumentation. Martin and Bookrajian (1962) analysed 81 cases of Gram-negative rod bacteria complicating pyelonephritis and found that in 78 the patients had previously undergone one or more forms of instrumentation of the urinary tract. In the majority of cases an indwelling catheter had been used, and the risks inherent in the presence of an indwelling catheter are known to be high. Kass (1957) showed that whereas the rate of infection after single catheterization was only 2% the presence of an indwelling catheter for 96 hours resulted in an infection rate of 98%. The use of a non-irritant catheter and an effective drainage system could be expected to reduce this incidence considerably, but none the less the difference is still marked, and figures which relate to the risk of infection with an indwelling catheter should not be regarded as being relevant when the dangers of diagnostic or therapeutic instrumentation are being considered.

Nevertheless, however small the risk, infection does occur after instrumentation, and every urologist must have seen examples of severe infections following apparently straight-

forward instrumental procedures. Can this risk be reduced by the administration of prophylactic drugs? Rehm (1962) performed a controlled study on 184 patients (the majority of whom were female) undergoing cystoscopy. The treated group were given sulphonamides for five days after cystoscopy, and a second sample of urine was taken two weeks later. In both control and treated groups two cases of bacteriuria were discovered (100,000 organisms per ml.), and the deduction was made that prophylactic drugs were not advisable. On the other hand, Davis *et al.* (1959) performed a similar study on obstetric patients catheterized during labour and found that 29% of the control group and only 11% of the treated group had bacterial counts of greater than 10,000 per ml. 72 hours after delivery. At this time the treated group were still receiving medication. Since the present study was performed largely on out-patients, it was felt desirable to give a single dose of a drug which could be taken under supervision and which would give protection at the time of instrumentation and for a period of 24 to 48 hours afterwards. The second specimen of urine was taken 72 to 96 hours later at a time when the level of antibiotic had fallen to insignificant levels but before a short-lived spontaneously subsiding infection was likely to have ceased to give evidence of its presence. It is apparent from the results of this study that the only patients who could be regarded as having benefited from the administration of the antibiotic were those in whom a preliminary urine culture, had one been taken, would have indicated the need for therapeutic drug administration and delay of the proposed instrumentation. The other instances of apparent improvement can probably be explained on the basis of the spontaneous variation in the level of bacteriuria which is known to occur in patients in whom this condition is established. Those patients who experienced symptoms but failed to show evidence of infection possibly suffered a transitory self-limiting infection, but it is more likely that these symptoms were the result of trauma to the urinary tract, since most of them followed such procedures as closed cystodiathermy or difficult posterior dilatation.

Every effort must, of course, be made to avoid the establishment of bacteriuria. Kaitz (1961) has shown that bacteriuria in pregnant women is associated with a significant diminution of urinary concentrating ability, and Turck *et al.* (1962) gave evidence of the difficulty of eradicating bacteriuria once established. This difficulty is known to be particularly marked in patients in whom there is a persisting abnormality of the urinary tract. All but three of the patients who were found in this study to have bacteriuria at the first visit had undergone many previous procedures, including in most cases open operation and either urethral or suprapubic catheter drainage, which would explain the development of bacteriuria in the first place. None of these patients has symptoms related to their chronic bacteriuria, but efforts are currently being made to eradicate the organisms in these patients. It is unlikely in several cases that it will be possible, and for this reason we would advise that efforts be made to detect bacteriuria at an early stage. The patients who require treatment can be detected by performing bacterial counts one or two weeks after instrumentation, and it is particularly important that this be done in those patients suffering from a persisting abnormality of the urinary tract such as papillomatosis or a urethral stricture. Energetic treatment can then be given before the organisms have become established. Beyond that the use of antibiotics in relation to instrumentation of the urinary tract seems to be inadvisable.

Summary

A controlled trial was carried out to assess the value of a single prophylactic dose of a long-acting wide spectrum antibiotic (demethylchlortetracycline) in instrumentation of the urinary tract. In all, 212 patients were surveyed, 105 in the control group, 107 in the test group.

Three conclusions were drawn from this study: (1) That the risk of inducing bacteriuria at urological instrumentation under the conditions described is low; (2) that this risk is not reduced by giving a single dose of a long-acting wide spectrum antibiotic; (3) that many cases of bacteriuria induced by instrumentation are self-limiting and therefore presumably of no serious consequence.

A comparison of the results of this survey and of the results of other work in this field shows that conclusions regarding the risks of infection resulting from instrumentation in obstetric patients, or resulting from the presence of an indwelling catheter, cannot be applied to the risks of instrumentation in urological patients.

I would like to thank Mr. G. C. Tresidder, who allowed me to carry out this survey on his patients and who gave me great encouragement and assistance in its organization. I would also like to thank Professor M. W. Weatherall, who advised on the method of planning the trial, and Professor C. Barwell, in whose department the bacteriological work was performed. My thanks

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Phrynoderma

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In 1933 Nicholls coined the term "phrynoderma" to describe a particular type of follicular hyperkeratosis seen in tropical countries. The elbows, thighs, and buttocks are characteristically affected, the follicles contain large keratin plugs, and the adjacent skin is usually darker than normal. Most workers have come to the conclusion that it is a disease of malnutrition, though the precise deficiency is still in doubt. Frazier and Hu (1931) claimed that cod-liver oil produced improvement, and Loewenthal (1933) and Rao (1937) attributed this to an increased intake of vitamin A. Nicholls (1934), Aykroyd and Krishnan (1937), and Gopalan (1947), however, thought that vitamin-B deficiency was responsible, and Gopalan pointed out that xerophthalmia did not correlate with phrynoderma, as would be expected if vitamin-A deficiency was the cause. Finally, some evidence that deficiency of essential fatty acid might be the cause was produced by Ramalingaswami and Sinclair (1953).

The opportunity was taken to study this problem during a year (1962–3) as a lecturer at University College Hospital, Ibadan, Nigeria.

Method

All patients with follicular hyperkeratosis seen in the skin clinic at University College Hospital were studied and those with obvious phrynoderma were selected. A general examination was made, their diet assessed, and blood taken for estimation of haemoglobin, white-cell count, and serum vitamin-A level, the method of Paterson and Wiggins (1954) being used.

All cases were then given oral therapy, first riboflavin (20 mg. daily for a month), then aneurine hydrochloride (6 mg.

daily for a month), and finally vitamin B co. forte *N.F.* (two tablets daily for a month; each tablet contains riboflavin 2 mg., aneurine hydrochloride 5 mg., nicotinamide 20 mg., and pyridoxine hydrochloride 2 mg.). Each patient was seen once a month.

Results

Of 432 Nigerians seen in the skin clinic during December 1962 to July 1963 39 had follicular hyperkeratosis. All were children. Four had id eruptions (three due to tinea capitis (*Microsporon audouinii*) and one to ulcerating glandular tuberculosis), 11 had a bizarre dyskeratosis of a striking distribution which was probably due to an inherited keratin defect (Shrank, 1966), and two had keratosis pilaris. The remaining 22 (5% of all skin patients) had phrynoderma; eight were boys and 14 were girls, with a mean age of 10 years (range 3 to 16).

The eruption had been present for a mean of eight months (range two weeks to one year) and involved the characteristic sites. There was no family history of a like eruption. All the children in this group seemed fit, with the exception of two who had stomatitis. Physical examination did not reveal any cause for the eruption, though three had palpable spleens due to chronic malaria.

Sixteen of the children were Yoruba and 23 were Ibo. Their diet was essentially the same and typical of the Western Region of Nigeria. It is composed mainly of the starchy roots—yam and cassava—supplemented with only small amounts of meat, beans, green vegetables, and fruit. Much of the food is cooked in red palm oil, which provides liberal amounts of linoleic acid (9.7% of the total fatty acids (Naismith, 1963)) and is the most potent natural source of carotene known (carotene content equivalent to 1,000–100,000 I.U. of vitamin A per 100 g. (Platt, 1962)). Evaluation of this

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