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THE RESULTS OF CHEMOTHERAPY IN URINARY INFECTIONS

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Twenty-five years ago the only available urinary anti-septic was hexamine. Since then the ketogenic diet, mandelic acid, the sulphonamides, and various antibiotics have successively become available, providing opportunities, or so it would seem, for the successful treatment of almost any infection which can arise. How successfully this wealth of therapeutic resources has been applied it is difficult to judge: in particular, further data seem desirable on the results of treatment with drugs more recently introduced and now in almost exclusive use.

Many reports describe the immediate good results which follow the treatment of infections of the urinary tract with modern antibacterial drugs. The longer the period after treatment, however, the more frequent is relapse or reinfection, and Stenderup *et al.* (1952) express a widely held view when they remark that, considering the present resources of chemotherapy, the results of treatment of urinary infections are not as good as might be expected. Stenderup and his colleagues, who treated 181 patients, found that relapse or reinfection occurred not only in patients with abnormal urinary tracts or a past history of infection but also, although less frequently, in patients with no obvious complicating factors.

The importance of obstruction in the ultimate outcome of treatment was clearly shown by Rhoads *et al.* (1952), in the treatment of 325 patients, more than 75% of whom had demonstrable urinary obstruction. They found that, while rather more than half their patients had sterile urine after treatment, only some 11% were permanently cured, and these were patients without obstruction originally or in whom the obstruction had been corrected.

Patients with infections of the urinary tract are numerous, and their study provides the laboratory with a considerable volume of work. This investigation was designed to take advantage of such routine material with a view to discovering how often laboratory sensitivity tests are likely to foretell the result of treatment when the patient is treated with a drug to which the infecting organism is sensitive.

Composition of Series

The series includes nearly all the adult patients with diagnosed urinary infections seen in the hospital between

September, 1952, and August, 1953, and is presented in outline in the accompanying Diagram. Some patients were treated by chemotherapy more than once during this period, and the 1,022 incidents derived from 686 patients represent the total number of patients seen either for the first time or after the failure of a previous course of treatment.

Patients seen more than once were included in the series only if presenting with a fresh infection or if still needing treatment for an infection which had failed to respond, and were not automatically included to swell the total figures. This has inevitably led to the repeated

Structure of the investigation

inclusion of patients with the same *condition* (for example, urinary tract abnormality), but less often to the inclusion of patients with the same *infection* (for example, infection with *Bacterium coli*). As will be seen in the results, treatment may fail to sterilize the urine although the original organism may often be replaced by another. Of the 686 patients, 500 figure only once, the remaining 186 patients being responsible for 522 incidents, an average of 2.8 incidents per patient.

Most of the after-treatment specimens of urine were examined within five days of the end of treatment, and

the majority of follow-up specimens two to four months later. All specimens were collected by catheter in females and aseptically in males. No attempt was made to influence clinicians in their choice of treatment except in so far as they were influenced by a report of sensitivity tests. Clinical information, which was not specially recorded for this survey, was taken from the patient's notes after discharge and, with the laboratory findings, was subsequently analysed by means of Hollerith punch cards. Tables I and II show the depart-

TABLE I.—Composition of the Series by Departments

Department	In-patients	Out-patients
General medicine	181	109
General surgery	298	146
Gynaecology and obstetrics	230	30
Other	5	23
Total ..	714	308

were filled with solutions containing penicillin 100 units/ml., streptomycin, chlortetracycline ("aureomycin"), oxytetracycline ("terramycin"), and chloramphenicol 250 µg./ml. Chlortetracycline solution was made daily; the remainder at intervals of one to two weeks, with storage at +4° C.

Sulphonamide sensitivity tests were done similarly, except that a special medium was used. This consisted of normal male urine, 1% glucose, and 2% agar, adjusted to pH 7, to which 5% of blood was added. On this appropriate medium, which is free from sulphonamide inhibitors, urinary organisms grew satisfactorily. Holes in this medium were filled with solutions of sulphadiazine, sulphathiazole, sulphadimidine (all sodium salts), and sulphacetamide, each of a concentration of 25 mg./100 ml. Sensitivities to all four drugs were measured for the first 254 organisms. It was found that in all but four instances the radii of the inhibition zones were, within experimental limits, in the same decreasing order, the mean values being sulphathiazole 7.3 mm., sulphadiazine 7.2 mm., sulphadimidine 5.8 mm., sulphacetamide 3.4 mm.

TABLE II.—Composition of the Series by Age, Sex, Clinical History, Duration of Symptoms, and Number Treated

	Sex	Total	Age †			Duration of Symptoms ‡			Treated by Chemotherapy
			Less than 35	35-64	65 or More	Less than 2 Weeks	2-8 Weeks	9 weeks or More	
With U.T.A.*	M	297	18	134	145	10	15	256	162 (55%)
	F	101	31	43	24	3	4	83	76 (75%)
Without U.T.A. but with history of previous infection	M	76	2	56	17	2	13	40	51 (67%)
	F	263	63	145	54	46	32	126	197 (75%)
Without U.T.A. and no history of previous infection	M	51	10	30	11	19	17	3	30 (59%)
	F	234	65	132	37	154	30	22	210 (90%)
Total ..	M	424	30	220	173	31	45	299	243 (57%)
	F	598	159	320	115	203	66	231	483 (81%)

* U.T.A. = Urinary tract abnormality.

† Omitting 5 patients of unknown age.

‡ Omitting 147 patients for whom this was not recorded.

ments of the hospital from which the patients were drawn and the age and sex distribution of all the patient-incidents encountered, together with the duration of symptoms, the number of patients with a previous history of urinary tract infection and with known urinary tract abnormalities, and the number treated by chemotherapy.

Dosage Schemes

Dosage schemes varied, but only in a few instances did they appear to be inadequate. Of patients who were given procaine penicillin 83% received 600,000 units or more daily, and of those receiving crystalline penicillin 94% were given 1,000,000 units or more daily. Of patients receiving streptomycin, 28% had 2 g. or more daily, while 98% had 1 g. or more. At least 1 g. of chlortetracycline was given daily to 98% of the patients being treated with this drug. A daily dose of 3 g. or more was given to 79% of patients receiving sulphonamides.

Analysis of the length of treatment of patients from whom an after-treatment specimen of urine was obtained, and who were treated with a single drug, showed that when penicillin was used it was given for at least four days in 90% of cases, aureomycin for at least four days in 93%, and sulphonamides for at least four days in 95%. All the patients treated with streptomycin received it for at least two days.

Laboratory Methods

All sensitivity tests were done by the agar diffusion method in primary culture. For tests with antibiotics three holes 8 mm. in diameter were cut with a sterile cork-borer in a blood-agar plate previously dried, and two in another. The plates were inoculated by uniform spreading with a bent glass rod of a 2-mm. loopful of urine and the cups

Thereafter the tests were done with sulphathiazole only, this being chosen in preference to sulphadiazine, which has a closely equivalent overall activity, because sulphathiazole was the only one of these drugs to which staphylococci were ever at all sensitive.

Reading of Results

The sensitivities to both antibiotics and sulphonamides were read as 0, +, ++, or +++ according to the width of the zone of inhibition produced. The approximate equivalents of these readings in terms of the minimum inhibitory concentrations were determined by testing a series of organisms in parallel by a tube dilution method, with the results in Table III. It is not pretended that this method is accurate

TABLE III.—Quantitative Significance of Degrees of Sensitivity Estimated

Degree of Sensitivity	Radius of Inhibition Zone	Equivalent Minimum Inhibitory Concentration*					
		Sulphathiazole	Penicillin	Streptomycin	Chlortetracycline	Chloramphenicol	Oxytetracycline
0	—mm.	>16	>10	>10	>20	>20	>20
+	2-5 "	4-8	5-10	2-5	5-10	10	10
++	6-10 "	2	2-5	1-2	2-5	2-5-5	2-5-5
+++	>11 "	<1	<1	<0.6	<0.6-1.2	1-2	<0.6-1.2

* For sulphathiazole in mg./100 ml.; for penicillin in units/ml.; for remainder in µg./ml.

or even that it was applied with strict accuracy: the width of the inhibition zones is so much affected by several factors, notably profusion of growth, that minute measurements of zones in such cultures is pointless. On the other hand, it is well suited by its simplicity and rapidity for routine use on a large scale and is unlikely to lead to gross error in experienced hands.

Bacteriological Findings

Of the 1,022 infections studied 881 were due to a single organism, 133 to 2, 7 to 3, and 1 to 4. The numbers of

10 identified species studied are stated in Table IV. It can be seen from this table that *Streptococcus faecalis* commonly occurred in association with another organism, 38% of infections with this organism being multiple; *Bact. coli*, on the other hand, commonly occurs alone, only 11% of infec-

TABLE IV.—Composition of the Series by Species* of Organism and Sex of Patient

	Total		Male		Female	
	Single	Multiple	Single	Multiple	Single	Multiple
<i>Bact. coli</i> ..	368	47	83	13	285	34
<i>Bact. coli</i> intermediate ..	39	10	20	7	19	3
<i>Bact. aerogenes</i> ..	17	7	9	3	8	4
Paracolon bacilli ..	56	27	50	26	6	1
<i>P. vulgaris</i> ..	62	19	22	11	40	8
<i>P. morgani</i> ..	39	25	37	24	2	1
<i>Ps. pyocyanea</i> ..	44	16	29	12	15	4
<i>Str. faecalis</i> ..	105	63	27	27	78	36
<i>Staph. pyogenes</i> ..	28	19	16	10	12	9
<i>Staph. albus</i> ..	66	18	27	7	39	11
Other organisms ..	57	39	24	28	33	11
Total infections ..	881	141	344	80	537	61

* Lactose-fermenting coliform bacilli were identified as follows: *Bact. coli* methyl red +, growth in citrate -; *Bact. coli* intermediate M.R. +, citrate +; *Bact. aerogenes* M.R. -, citrate +. Non-lactose-fermenting coliform bacilli were classified by mannite fermentation, indole production, and formation of H₂S, paracolon bacilli being mannite±, indole+, and H₂S -; *P. morgani* mannite-, indole±, and H₂S+. The remaining species were identifiable by more obvious characters, except that coagulase production was used to distinguish the two species of staphylococci.

tions being multiple. Further analysis of the types of infection occurring together revealed nothing of apparent significance.

The distribution of organisms by sex is shown in the same table. A notable feature here is the preponderance of females in *Bact. coli* infections, and to a smaller extent in those due to *Str. faecalis*. On the other hand, paracolon bacilli, *Proteus morgani*, and *Pseudomonas pyocyanea* occur more commonly in males than in females. These differences are presumably related to the route by which bacteria reach the urinary tract. The common organisms in the female are those predominating in the lower bowel, and an ascending infection from the ano-genital region would explain this. Such a mechanism is unlikely in the male, but alternative routes which would account for the difference in flora could only, in the present state of knowledge, be suggested on a purely speculative basis.

The percentages of strains of all identified organisms found in culture to be resistant to each drug are stated in Table V.

TABLE V.—Percentages of Organisms Resistant (0 or +) to Six Drugs

	Total No. of Orgs.*	Percentage resistant (0 or +) to:					
		Penicillin	Streptomycin	Chlorotetracycline	Chloramphenicol	Oxytetracycline	Sulphathiazole
<i>Bact. coli</i> ..	414	99	10	13	9	5	11
<i>Bact. coli</i> intermediate ..	49	98	45	23	19	11	43
<i>Bact. aerogenes</i> ..	24	96	21	21	17	17	38
Paracolon bacilli ..	83	100	90	72	75	67	94
<i>P. vulgaris</i> ..	81	52	23	89	22	89	28
<i>P. morgani</i> ..	63	52	90	78	32	76	100
<i>Ps. pyocyanea</i> ..	60	100	73	85	93	80	97
<i>Str. faecalis</i> ..	167	17	87	18	9	18	100
<i>Staph. pyogenes</i> ..	47	77	40	9	9	9	100
<i>Staph. albus</i> ..	83	19	25	12	10	13	85

* The figures in this table do not exactly correspond with those in Table IV as a small number of organisms were not tested for sensitivity.

Some entries in this table merely illustrate natural resistance, such as that of *Ps. pyocyanea* to penicillin and of *Str. faecalis* to sulphonamides. Others afford some guide to the likelihood of success in treatment and presumably indicate the extent to which resistance has been acquired in consequence of past use of drugs in this country. The most generally resistant organisms are paracolon bacilli, *P. morgani* and *Ps. pyocyanea*, and this property, as will be seen later, is reflected in therapeutic results. Both *P. morgani* and *P. vulgaris* are unlike other Gram-negative species in being

frequently sensitive to penicillin. Most strains of *Staphylococcus pyogenes* are penicillin-resistant but usually sensitive to chlortetracycline, oxytetracycline, and chloramphenicol. Resistance to these drugs is also less common among Gram-negative bacilli than it has been reported to be in the United States (Romansky *et al.*, 1951) and Australia (Thomson, 1952), but the results of widespread habituation are evident in the findings for streptomycin and sulphathiazole.

An indication of the changes in sensitivity during the period of treatment is given by a study of the 103 organisms which were recorded as being present in the urine before and immediately after treatment, and for most of which two sets of sensitivity tests to the six drugs were carried out. Out of the 593 pairs of readings there was no change in 427 (72%), a decrease in sensitivity in 90 (15%), and an increase in 76 (13%). These findings are analysed in more detail in Table VI, which shows the original sensitivity and the degree of change—two steps being, for instance, a change from 0 to ++. It will be seen that the majority of changes were of only one step; technical faults or misinterpretation may be responsible for most of these. Decreases in sensitivity of more than one step were mostly due to the drug

TABLE VI.—Changes in Sensitivity to 6 Drugs of 103 Organisms Tested Before and Immediately After Treatment

Initial Sensitivity	Total	No Change	Increased Sensitivity			Decreased Sensitivity		
			One Step	Two Steps	Three Steps	One Step	Two Steps	Three Steps
0	267	246	7	11	3	—	—	—
+	28	11	9	3	—	5	—	—
++	151	78	43	—	—	12	18	—
+++	147	92	—	—	—	32	9	14
Total * ..	593	427	59	14	3	49	27	14

* In 25 instances one of the pair of sensitivities was not tested, and these are omitted from the table.

used in treatment, often streptomycin. Increases may sometimes have been actual (increased sensitivity to an antibiotic after exposure to another has repeatedly been observed): another possibility is the elimination of the original strain and the substitution of another.

Results of Treatment

The criterion of cure used in this investigation was the elimination of all organisms from the urine, and it has been applied to the results immediately after treatment and to the follow-up results. An after-treatment specimen of urine was obtained from 562 of the 726 patients treated with chemotherapy, and, although the number of patients from whom no specimen was received is larger than might have been hoped, knowledge of the circumstances and a comparison of some of the factors recorded induce us to believe that this has led to no gross selection. Follow-up specimens were examined from 317 of the 512 treated patients known to be alive and who either were free from infection immediately after treatment or from whom no after-treatment specimen was obtained. No attempt was made to follow up the 296 untreated patients or the 184 who were still infected after treatment.

Results in Relation to the Patient's Condition

As past experience and a preliminary examination of our results showed that the condition of the patient was the main factor in determining the outcome of treatment, treated patients have been divided into three categories—those with urinary tract abnormalities, those without abnormalities but with a past history of urinary infection, and the remainder in whom no abnormality was demonstrated and who gave no history of previous urinary infection. In the first and second groups the same patient may appear as two or more separate incidents, but the third group, by definition, cannot include more than one incident for each patient. Table VII shows the number in each group together with their ages,

TABLE VII.—Immediate Cure Rates of 562 Treated Patients, Showing Age, Sex, Clinical History, etc.

	Sex	Total	Age †			Duration of Symptoms ‡			Catheterized Within Previous Month	Cured
			Less than 35	35–64	65 or More	Less than 2 Weeks	2–8 Weeks	9 Weeks or More		
With U.T.A.*	M	116	7	51	58	4	11	97	79	39 (34%)
	F	55	19	22	14	1	2	49	35	32 (58%)
Without U.T.A. but with history of previous infection	M	34	—	27	6	—	6	19	13	16 (47%)
	F	159	32	93	34	31	20	79	100	118 (74%)
Without U.T.A. and no history of previous infection	M	20	3	14	3	3	10	1	1	16 (80%)
	F	178	54	101	23	120	21	17	118	157 (88%)
Total	M	170	10	92	67	12	27	117	93	71 (42%)
	F	392	105	216	71	152	43	145	253	307 (78%)

* U.T.A. = Urinary tract abnormality.

† Omitting 1 patient of unknown age.

‡ Omitting 66 patients for whom this was not recorded.

the proportion catheterized in the preceding month, the length of the current infection, and the immediate results of treatment.

It was at once clear that we were dealing with groups of uneven size and that direct comparison of the results of treatment of males and females will be invalid. The men were older, and those with urinary tract abnormalities predominated, while the largest groups of women were those with no abnormality, many of these (144) being gynaecological patients with a post-operative infection. The adverse effect of abnormalities or a previous infection is, however, demonstrated in each group.

Results in Relation to the Infecting Organism

Table VIII shows the immediate cure rates for multiple infections and for infections due to single organisms when the latter were treated with a drug to which the organism was sensitive or found subsequently to be resistant. The most striking feature is perhaps the number of patients

is made for this by using the three clinical categories, the same relationship between the cure rate for the three types of organism holds good. This is shown in Table X, which shows in addition that the corresponding rate for resistant organisms also follows the same pattern.

TABLE X.—Immediate Cure Rates of Treated Patients* by Type of Organism and Clinical History

	Type of Organism		
	Coccal	Coliform	Others
Sensitive organisms:			
Patients with U.T.A.	15/21 (71%)	28/49 (57%)	16/41 (39%)
Patients without U.T.A. but history of previous infection	16/19 (84%)	79/104 (76%)	20/31 (65%)
Patients without U.T.A. and no history of previous infection	52/56 (93%)	81/91 (89%)	13/18 (72%)
Resistant organisms:			
All patients	13/19 (68%)	7/17 (41%)	6/28 (21%)

* Omitting patients with multiple organisms.

Results in Relation to the Drug Used

Analysis of the results of treatment according to the drug used has failed to produce clear evidence of the superiority of one drug to another. Judging by the immediate cure rates, without taking other factors into consideration, "sulphatriad," sulphadimidine, and penicillin were most successful, curing 85, 82, and 81% of patients respectively. Sulphathiazole cured 78%, while of the patients treated with chlor-tetracycline, streptomycin, and sulphacetamide, 76, 69, and 50% respectively were cured. Bald presentation in this form is, however, misleading. Nearly all the patients, for instance, to whom sulphacetamide was given had abnormalities of the renal tract, and some of the apparent failures of aureomycin can also be accounted for in this way. The figures for streptomycin may also be fallacious, as there was no certainty that this drug was always withheld until the urine had been made alkaline.

Elimination of Specific Organisms from the Urine

As the aim of treatment is the cure of the patient, it is unrealistic to assess chemotherapy by its ability to remove a specific organism from the urine without at the same time producing a sterile urine. It should, however, be mentioned that of the 148 patients with a single infection whose urine was not sterilized, in as many as 68 (46%) the original organism was eliminated only to be replaced by another. It has not been possible to establish any clear connexion between this phenomenon and the clinical condition. It was as liable to happen in uncomplicated infections as in others, and, what is more, occurred as often when the original organism was resistant to the drug used in treatment as when it was sensitive.

Infections due to *Str. faecalis*

Evidence was obtained that catheterization and previous treatment with sulphonamides increased the likelihood of a urinary infection being due to *Str. faecalis*.

Of 157 women with urinary infections due to a single organism who had been given sulphonamides in the month

TABLE VIII.—Immediate Cure Rates of Treated Patients by Sensitivity of Organism to Drug Used in Treatment

	Sex	Single Organisms *		Multiple Organisms
		Sensitive (+ + or + + +)	Resistant (0 or +)	
With U.T.A.	M	22/47 (47%)	5/29 (17%)	4/24 (17%)
	F	27/44 (61%)	2/4	1/3
Without U.T.A. but history of previous infection	M,F	108/143 (75%)	11/21 (52%)	8/18 (44%)
Without U.T.A. and no history of previous infection	M,F	144/162 (89%)	8/10	19/23 (83%)

* Omitting 34 patients with a single organism but treated with multiple drugs.

cured even although treated with an inappropriate drug. The figures are small but presumably represent the natural cure rate, although it should be pointed out that six of the patients with no adverse history and treated with an inappropriate drug had coccal infections, which, as will be seen, are most easily cured.

Table IX shows the cure rate of infections due to individual species of organisms when these were sensitive to the drug. The better response of coccal infections is in part due to the fact that they were more frequent among the clinically favourable cases, but even when allowance

TABLE IX.—Immediate Cure Rates of Treated Patients by Species of Organism*

<i>Str. faecalis</i>	52/58 (90%)
<i>Staph. pyogenes</i> and <i>albus</i>	31/38 (82%)
Coliform †	188/244 (77%)
<i>P. vulgaris</i>	18/30 (60%)
<i>P. morgani</i>	2/11
Paracolon bacilli	6/13
<i>Ps. pyocyanea</i>	5/10
Other organisms	18/26 (69%)

* Omitting multiple organisms, and organisms resistant (0 or +) to the drug used in treatment.

† *Bact. coli*, *Bact. coli* (intermediate), and *Bact. aerogenes*.

prior to examination and who had also been catheterized, 45 (29%) were infected with *Str. faecalis*, as were 3 of the 11 patients who had been given sulphonamides only. Twenty-seven of the 189 women (14%) who had been catheterized but had not received sulphonamides developed a *Str. faecalis* infection, whereas only 3 of 169 (2%) who had neither been catheterized nor received sulphonamides were so infected. The figures for men showed a similar trend.

Follow-up Results

The failure to obtain a follow-up specimen from a comparatively large number of patients was disappointing, but there is no reason to suppose that it materially altered the results. Patients not followed included many of the older patients (particularly if living outside London), and to this extent the cure rates may be too high. On the other hand, the inclusion of many of the more complicated cases would tend to depress the rate.

Table XI shows the patient's condition to be of prime importance and the main factor in determining the cure rate. Even among uncomplicated cases, however, and to a greater extent among the patients with a past history of infection but no demonstrable abnormalities, an appreciable number were found to be infected at the follow-up.

TABLE XI.—Comparison of Immediate and Follow-up Results

	Sex	Immediate		Follow-up *	
		No. of Patients	No. with Sterile Urine	No. of Patients	No. with Sterile Urine
Patients with U.T.A.	M	116	39	58	15
	F	55	32	27	7
Patients without U.T.A. but history of previous infection {	M	34	16	16	10
	F	159	118	79	51
Patients without U.T.A. and no history of previous infection {	M	20	16	11	9
	F	178	157	126	113

* The figures in these columns exclude patients with an infected urine after treatment but include some from whom no after-treatment specimen was obtained. This accounts for the fact that, in one instance, the number of patients followed up is greater than the number shown as sterile in the previous column.

There were a few patients whose urine after treatment was sterile but nevertheless contained pus. No evidence was obtained that these patients were more likely to be infected at follow-up than patients whose urine contained neither pus nor organisms.

Discussion

This paper is based on the practice of this hospital over 11 months, as seen from the laboratory, and while this viewpoint has advantages it also has disadvantages which will already be apparent. Some 80 doctors were able to contribute patients to the survey, and inevitably treatment varied with personal preferences. The most serious result of this is that the frequency with which patients were seen after treatment has varied and the results are less clear-cut than they might have been if all the patients had been treated in accordance with a common plan. Nevertheless certain facts have emerged.

The most striking is the confirmation of previous reports that, despite the undoubted efficacy of modern antibacterial drugs, chemotherapy usually fails to sterilize the urine of patients with abnormalities of the urinary tract, and that in the absence of a demonstrable abnormality a history of previous infection also reduces the likelihood of cure, although to a lesser degree. While in some instances the drug could hardly be blamed for this failure, as the original organism was eliminated only to be replaced by another, in general it presumably represents the inability of the sulphonamides and antibiotics to deal effectively with bacteria in the circumstances peculiar to an obstructed renal tract.

Treatment of patients with uncomplicated infections is more satisfactory, but even here an appreciable number were found to be still infected immediately after treatment,

and of those with sterile urine at this time a few were again infected some months later. All these groups of patients demonstrated the value from the patient's point of view of a re-examination some months after apparently successful treatment.

It was also clear from the patients' notes that some infections were relatively or completely symptomless and that under the conditions of a busy out-patient department it was not always possible to exclude urinary infection by naked-eye inspection of a sample of urine. If these observations apply to patients treated in other places, it would seem reasonable to suggest that to avoid chronic renal infection with its attendant dangers the cure of patients treated for urinary tract infections should be confirmed by microscopical examination of the urine both after treatment and again some months later.

Turning to what must be regarded as less important factors, there seems to be little to choose between the six drugs most commonly used in this investigation—sulphatriad, sulphadimidine, sulphathiazole, penicillin, streptomycin, and chlortetracycline. On grounds both of efficacy and expense, and possibly of lack of toxicity, the sulphonamides clearly keep their place in the treatment of urinary infections. The position of sulphacetamide is uncertain. Its activity *in vitro* suggests that it would be the least effective of the sulphonamides, and superficially our results support this. As, however, only a small number of patients were treated with it, and most of these had obstructive lesions, the finding that sulphacetamide had the lowest cure rate of all the drugs employed cannot be accepted as a true indication of its value.

It is clear (Table IX) that prognosis depends much on the species of organism, coccal infections responding best, those due to *Bact. coli* and closely related species well, whereas other organisms can less often be eliminated. There is also a clear relationship (Table VIII) between the sensitivity of the organism and the outcome of treatment, although some patients recover despite the use of an inappropriate drug. Laboratory examination, including sensitivity tests, can evidently improve the chances of successful treatment substantially. It distinguishes in the first place between coccal and coliform infections, the appropriate treatments for which differ unless a "broad spectrum" antibiotic is used: secondly, it takes account of strain variations in sensitivity among individual species. As may be seen from Table V, the number of strains, even of commoner bacteria, abnormally resistant to sulphonamides and to those antibiotics particularly which have been longer in use, is far from negligible.

Summary

Clinical and laboratory findings in 1,022 urinary infections occurring in 686 adult patients are given with particular reference to the presence of urinary tract abnormalities and a past history of urinary infection, and to the species of organism(s) present and their sensitivity to sulphonamides and to five antibiotics.

Of these infections 726 were treated with chemotherapy and the results of treatment assessed by examination of after-treatment and follow-up specimens of urine, using absence of organisms from the urine as the criterion of cure. After-treatment specimens obtained from 562 patients showed that, while the prognosis was good in patients with no urinary tract abnormalities and no history of urinary infection (16/20 males and 157/178 females being cured), it was indifferent in patients with a previous history of urinary infection (16/34 males and 118/159 females being cured) and poor in patients with a definite urinary tract abnormality (only 39/116 males and 32/55 females being cured). The follow-up findings confirmed this and showed the necessity for examining the urine some months after treatment if the results are to be assessed correctly.

Among less important factors affecting cure, coccal infections were shown to respond best, those due to *Bact. coli* and *Bact. aerogenes* well, whereas infections due to *Proteus*, *Ps. pyocyanea*, and paracolon bacilli were more resistant to treatment. There was a clear relationship between the *in vitro* sensitivity of the organism and the outcome of treatment, and the use of laboratory sensitivity tests is advocated to avoid the prescription of inappropriate drugs. For most species identification only is no longer sufficient. No clear evidence was obtained that any one of the drugs used most often (sulphatriad, sulphadimidine, sulphathiazole, penicillin, streptomycin, and chlortetracycline) was superior to the others.

We are grateful to our clinical colleagues for permitting us to use the material on which this investigation is based, and particularly to the Medical and Surgical Registrars for their collaboration. Among those who have been involved in heavy additional work we wish particularly to thank Miss E. J. Armour for tracing patients' records, and Mr. R. Andrew, Miss M. Rhodes, and Miss P. M. Waterworth for laboratory assistance.

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FAILURE OF SULPHONAMIDES TO PREVENT URINARY INFECTIONS AFTER VAGINAL SURGERY

BY

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Urinary infections occur frequently in patients undergoing vaginal operations, and sulphonamides are often given for their prevention. As the majority of these infections are due to *Streptococcus faecalis*, an organism resistant to sulphonamides, or to coliform bacilli, many of which nowadays are also resistant, the value of this form of treatment is likely to be limited. This paper is an account of a trial designed to test this conclusion.

Procedure

The trial lasted from February 1, 1953, until January 31, 1954, and was conducted in two wards (A and B). For the first three months patients admitted to ward A for vaginal operations (detailed in Table I for the whole series) were given 1 g. of "sulphatriad" three times a day for the first seven days after operation, patients in ward B receiving no such special treatment. At the end of three months the arrangement was reversed, patients in ward B receiving sulphatriad, while no prophylactic treatment was given to patients in ward A, and this alternation was continued for one year. Administrative reasons precluded a closer method of control, such as the use of alternate patients.

Catheter specimens of urine were collected from patients from both wards in the theatre before operation and again

on the tenth post-operative day, or earlier if indicated by the patient's clinical condition. In all, 117 patients were involved. Of these, 15 were excluded (6 infected before operation, 8 because specimens of urine were not examined, and 1 who was treated with penicillin for a wound infection), leaving in the trial the 102 patients described in Table I.

TABLE I.—Composition of the Series

	Test Group (Sulphonamide Given)	Control Group (No Sulphonamide)
Number of patients	60	42
Mean age	53 years	52 years
Age range	28-76 years	32-73 years
Ward A	33	18
" B	27	24
Diagnosis		
Prolapse with stress incontinence ..	25	20
" without "	24	17
Stress incontinence	6	2
Menorrhagia	4	3
Leucoplakia	1	—
Operation		
Colporrhaphy	47	36
Vaginal hysterectomy	10	6
Sling operation	2	—
Vulvectomy	1	—

Post-operative Catheterization

Three different procedures were adopted. Some patients were allowed to pass water unaided, or were catheterized if necessary. Others were left with an indwelling Malecot catheter, which was spigoted, the spigot being removed at approximately three-hourly intervals. The remainder were left with an indwelling catheter which drained into a jar containing 1/1,000 acriflavine. For several patients both methods of indwelling catheterization were used, but except in four instances it has been possible to classify the patients according to the type of catheterization predominantly employed. Table II shows how patients treated by these

TABLE II.—Methods of Catheterization

	Total	Ward A	Ward B	Test Group	Control Group
Indwelling catheter:					
With drain	53	36	17	30	23
" spigot	28	6	22	16	12
No indwelling catheter	17	6	11	11	6
Not classified	4	3	1	3	1

three methods were divided between the two wards and between the test and control groups. On an average indwelling catheters were retained for four days, after which patients were catheterized twice daily for three more days. The patient subject to most manipulation was one who, in addition to five days' drainage by an indwelling catheter, required catheterization 24 times. At the other end of the scale, of the patients left initially to pass water unaided, six never required catheterization.

Results

Table III shows the proportions of test and control patients with urine free from bacteria after operation, set out by wards and according to methods of catheterization. It

TABLE III.—Proportions of Patients Free from Infection after Operation

	Test Group (Sulphonamide Given)	Control Group (No Sulphonamide)
Total	9/60 (15%)	3/42 (7%)
Ward A	2/33	0/18
" B	7/27	3/24
Indwelling catheter		
With drain	2/30	0/23
" spigot	3/16	1/12
No indwelling catheter	4/11	2/6