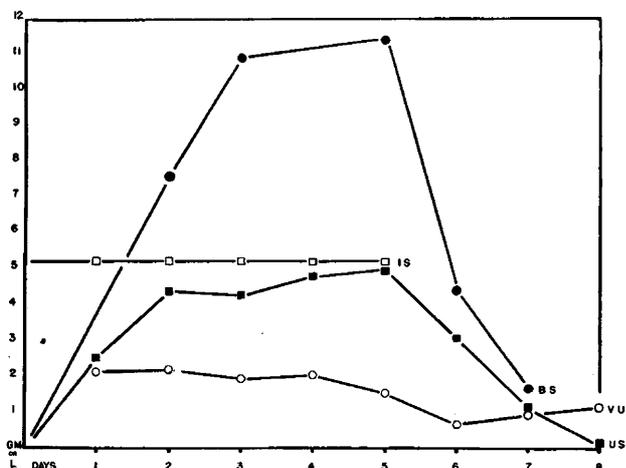


room temperature is less than 0.8 per cent, while at body temperature it is only about 1.1 per cent.³ Acetylated sulfanilamide we find considerably less soluble.⁴ Urinary concentrations were in these ranges in the cases under study. No data on solubilities of free and acetylated sulfanilamide in urine are available, but in several instances we have observed precipitation of acetylated sulfanilamide in urine at room temperature soon after collection. Urine at body temperature would certainly have greater power to hold the drug in solution, but nevertheless the possibility of stone formation in the urinary tract or blockade of renal tubules, where large doses of the drug are given and urine volume is small, seems real. This subject is being studied further.

SUMMARY

1. Recovery of administered sulfanilamide has been studied on a quantitative basis in patients without cardiovascular, renal or hepatic disease and without evidence of infection.
2. Rates of clearance through the urine of conjugated and free sulfanilamide of the blood have been determined.
3. The effect of water diuresis on rate of clearance of conjugated and free sulfanilamide has been investigated.



Sulfanilamide balance study in case 5. IS, sulfanilamide intake in grams per day; US, sulfanilamide content of urine in grams per day; VU, daily urine volume in liters; BS, total sulfanilamide concentration of whole blood in milligrams per hundred cubic centimeters plotted on the ordinate scale.

4. Concentrations of conjugated and free sulfanilamide in blood and urine during a period of water abstinence have been noted.

CONCLUSIONS

1. In man sulfanilamide is excreted almost entirely by the kidneys, in either the free or the conjugated form.
2. The concentration of free and conjugated sulfanilamide in the blood resulting from a given per pound dosage is quite variable in different individuals; hence the importance of frequent determinations of blood level during intensive therapy with the drug.
3. After sulfanilamide has been stopped the drug is rapidly eliminated from the body, provided renal function is normal and urine volume adequate.

4. The concentration of conjugated sulfanilamide in the blood is much lower than that of the free sulfanilamide.

5. The rate of clearance of conjugated sulfanilamide is greater than that of free sulfanilamide.

6. Water diuresis increases the rate of urinary excretion of both forms of the drug.

7. The precipitation of excreted sulfanilamide in urine at room temperature has been demonstrated, suggesting the possibility of formation of stones in the urinary tract should urine volume become too small during sulfanilamide therapy.

USE OF SULFANILAMIDE AFTER TRANSURETHRAL PROSTATECTOMY

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The successful results that have accrued from the use of sulfanilamide in the treatment of infections of the urinary tract have prompted a survey of its utility in postoperative management of cases in which transurethral prostatic resection has been performed.

At least half of the persons presenting themselves for this operation have grossly infected urine. Only rarely do we endeavor to treat such infections prior to operation. Postoperative febrile reactions which may be traced to such infections occur infrequently in our cases and we believe that the offending bacterial organisms responsible in cases manifesting febrile reactions were probably introduced at operation and are not strains of bacteria previously harbored by the patient.

The study promised to be attractive because it was of a group of persons of the same sex, of approximately the same age, and all suffering from an obstructive lesion which gave rise to a similar sequence of clinical and pathologic events. The number of patients was sufficient to group into a control series and an experimental series, each to receive substantially identical treatment with the exception of the urinary antiseptic concerned.

The average period of postoperative hospitalization of the patients was five days and therefore it was decided that specimens of urine should be collected for examination at the time of operation and on the fifth postoperative day. Administration of the drug was begun on the morning of operation and was continued until the fifth day after operation.

COLLECTION AND BACTERIOLOGIC STUDY OF THE URINE

Each specimen of urine was obtained by catheterization under aseptic technic on the first and fifth days. The specimen was kept in the ice box until cultures were taken from four to six hours later. After the sample of urine had been mixed thoroughly, seedings were made on the surface of blood agar plates; these were incubated for twenty-four hours at 37.5 C. Subsequently, smears of the colonies growing on the plates were made and were stained by Gram's method and the results were recorded under the three broad headings

3. Allport, N. L.: Para-Amino Benzene Sulfonamide, Quart. J. Pharmacy & Pharmacol. 9: 560 (July-Sept.) 1936.

4. Unpublished data.

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of gram-negative organisms, streptococci, including diplostreptococci, and micrococci, including staphylococci.

ADMINISTRATION OF SULFANILAMIDE

Every other patient admitted to the hospital was given the drug, and the alternate patients were used as controls. Discrimination was not made as to which patients should receive sulfanilamide. The dose ranged

TABLE 1.—Results of Culture of Urine on Day of Operation and on Fifth Postoperative Day

Results	Transurethral Prostatectomy, Thompson, 1934, 200 Cases, per Cent	1937 Series	
		Control, 100 Cases, per Cent	Sulfanilamide, 100 Cases, per Cent
1. Same organisms on first and fifth day	36	33	16
2. Culturally negative throughout	11.5	15	25
3. Change in bacterial flora between first and fifth day	14	16
4. Additional organisms on fifth day not present initially, excluding those itemized in 3.....	36	32
5. Organisms not present on first day but found on fifth day; items 3 and 4 together	47	50	48
6. Became culturally negative..	5.5	7	20
Types of organisms found on fifth day:			
Gram-negative organisms..	42	34	16
Streptococci	32	23	12
Micrococci	36	34	31

between 45 and 60 grains (3 and 4 Gm.) daily, and the majority of the patients receiving this medication also were given a similar amount of sodium bicarbonate. No effort was made to establish a urine of a particular hydrogen ion concentration.

Because of nausea, cyanosis, skin reactions and even low grade fever, it was necessary to discontinue administration of the drug in nine cases. We present data on 100 patients who received sulfanilamide and an equal number, the control group, who received no urinary antiseptic whatever. We have available for comparison the bacteriologic observations in a similar group of 200 cases of transurethral prostatectomy compiled by Thompson¹ in 1934.

Table 1 brings out the close similarity as regards both the number of specimens of urine infected and how these infections behaved during the stage of post-

TABLE 2.—Summary of Bacteriologic Observations

	Control Series, per Cent	Sulfanilamide Series, per Cent
Infected urine, day of operation.....	48	51
Infected urine, five days after operation....	77	55
Uninfected urine, remaining sterile.....	15	25
Uninfected urine, becoming infected.....	28	18
Infected urine, becoming sterile.....	7	20

operative hospitalization. Further, the types of organisms found in the series of 1934 were substantially as frequently encountered then as in 1937.

The sulfanilamide series brings out two apparent changes that we will mention at this time. First, there seems to be some general bactericidal action directed toward those organisms originally present in the urine. Second, a greater percentage of initially "sterile" urines remain culturally negative.

To proceed with a general survey of the results of administration of sulfanilamide on the urine, table 2 illustrates the infected (culturally positive) and the sterile (culturally negative) specimens of urine and their behavior during the course of the experiment.

Table 2 shows that an equal number of patients have infected urine initially in the respective groups. Five days later, however, among those patients receiving sulfanilamide, there is a drop in the percentages of infected specimens of urine and a larger number of uninfected specimens remain "sterile."

At this point we should discuss two important facts brought out by the two tables. First, in table 1, as indicated already, there seems to be some general bactericidal action directed toward those organisms originally present in the urine. A consideration of side headings 3, 4 and 5 shows that this does not seem to be true of additional organisms that have become established in the urine following operation. There is no significant difference in the percentages of these newcomers in the control series as compared with the sulfanilamide series.

There occur to us two possible explanations: 1. The additional organisms are contaminants. This we cannot believe, because the organisms now in the fifth day

TABLE 3.—Organisms Present in Urine on Fifth Day

	Control Series, per Cent	Sulfanilamide Series, per Cent
Organisms present on culture on fifth day:		
Gram-negative bacteria	34	16
Streptococci	23	12
Micrococci	34	31
Uninfected urine, became infected with:		
Gram-negative bacteria	35	18
Streptococci	32	29
Micrococci	46	58

urines were found in numbers easily demonstrated by Gram's stain of the urinary deposit, thus excluding the probability of their being contaminants introduced at the time of collection of these samples. 2. On the other hand, we might postulate that this drug acts not only as a bactericidal agent alone but also in some way reinforces the mechanism of immunity operating against chronic infection. The new invader, introduced at the time of operation, has not had time, within the limits of the experiment, to call forth a defense reaction on the part of the host and therefore it has only the bactericidal action of the drug to contend with. Clinical experience in the management of urinary infections would lead us to believe that administration of sulfanilamide is frequently followed by a more dramatic improvement in the chronic infection than we observe among cases of acute infection. The mechanism of operation of sulfanilamide as yet is unsettled. The hypothesis that it acts by stimulation of some mechanism closely related to the natural immunologic defenses of the subject has been expressed by many writers, particularly those in England and on the continent of Europe. Our evidence seems to confirm this hypothesis.

In table 2 the second item might indicate that sulfanilamide inhibits establishment of organisms in the urinary tract. This, however, would be an erroneous conclusion as reference to table 1 demonstrates. It is not necessarily specimens of urine from the same

1. Thompson, G. J.: The Prevention of Complications of Transurethral Prostatic Resection, Urol. & Cutan. Rev. 38: 847-851 (Dec.) 1934.

patient, found to be infected on the day of operation, that we find infected on the fifth postoperative day.

The survey, up to the present, would indicate that a group of these patients, as a whole, would benefit from routine administration of this particular urinary antiseptic. It behooves us, therefore, to study the more detailed results of this therapy. In table 3 an analysis of the type of organisms present on the fifth day is presented.

The results of the cultures of these fifth day specimens would indicate that the effect of sulfanilamide is directed toward both gram-negative bacteria and streptococci and that the efficacy of this antiseptic in suppressing both of these organisms is about the same. Micrococci were found in about a third of the specimens examined irrespective of sulfanilamide.

Furthermore, micrococci found in the urine on the fifth postoperative day were not found in the urine prior to operation in 79 per cent of the sulfanilamide series and in 71 per cent of the control series. So far as these bacteria are concerned, they appear quite unaffected by administration of sulfanilamide. In the specimens of infected urine obtained five days after operation that were found to harbor micro-organisms not demonstrated in cultures of urine obtained on the day of operation, bacteria were demonstrated as shown in table 4, which gives the relative frequency with which these new invaders occurred in specimens of urine collected on the fifth postoperative day.

TABLE 4.—Frequency of New Invaders Present in Urine on Fifth Postoperative Day

Organisms	Control Series, per Cent	Sulfanilamide Series, per Cent
Gram-negative bacteria	45	57
Streptococci	84	73
Micrococci	71	79

We can only conclude from these results that strains of organisms gaining foothold after operation are not influenced by administration of sulfanilamide, although it would seem, from earlier tables, that the actual number of infected specimens is decreased following its administration.

A discrepancy was found between cultural results and microscopic examination of the sediment obtained by centrifuge in a number of the specimens. Pus cells in these specimens were demonstrated; however, there was no evidence of bacteria on culture. Without disputing the concept of amicrobic pyuria, it is evident that such observations must be laid to faulty technic in culturing the organisms, but the interesting fact is that this discrepancy is nearly four times as frequent in the group receiving sulfanilamide (table 5) as in the control group.

This considerable group of purulent specimens found to be culturally negative in the experimental series makes us doubt that they are, indeed, really sterile. We must neglect for the moment the considerable number of "amicrobic pyurias" in the control group and seek some explanation of this phenomenon of increase in the number of such specimens in the sulfanilamide group.

All the patients in this group received the drug up to the time when the second specimen of urine was collected and we are faced with the possibility that excretion of sulfanilamide in the urine of these subjects effected a bacteriostatic influence when it was attempted to culture these specimens on the usual mediums.

It has already been pointed out that, in a number of instances, it had been necessary to discontinue sulfanilamide and, in table 6, an attempt has been made to correlate the bacteriologic observations with administration of the urinary antiseptic in these cases.

The differences in the amounts of the drug given were quite insignificant and cannot explain the changes noted in the status of the specimens of urine. Of the nine cases in which it was necessary to discontinue use

TABLE 5.—Pyuria

	Control Series, per Cent	Sulfanilamide Series, per Cent
Purulent urine with negative cultures.....	12	44
Purulent urine with positive cultures.....	88	56

of sulfanilamide because of undesirable sequelae, four remained sterile throughout, three originally negative culturally became infected, and two of the specimens originally infected became negative on culture, five days after operation.

COMMENT

If there is any case for sulfanilamide, as used in the present series, it would seem to rest on a very frail foundation. We have failed to prove conclusively that there is a reduction in the number of infected specimens of urine after the drug has been taken for five days. The observation that the urine specimens of patients who were taking sulfanilamide give a higher percentage of negative cultures than do those of the control group is not necessarily conclusive. It means only that the methods used in this study for demonstration of the infecting organisms were inadequate. It would be necessary to allow several days to elapse after discontinuing the drug before the urine then obtained could be pronounced culturally negative. It is entirely possible that the presence of sulfanilamide in the specimens of urine that were cultured exerts a bacteriostatic effect and the methods of culture which were employed could not, therefore, exclude viable organisms.

The case against sulfanilamide as a routine urinary antiseptic in such postoperative cases is supported by the nine instances in which undesirable reactions have

TABLE 6.—Correlation of Bacteriologic Observations with Dosage of Drug

Bacteriologic Observations	Average Total Dosage of Sulfanilamide, Grains
Uninfected urine remaining sterile.....	156
Uninfected urine becoming infected.....	149
Infected urine becoming sterile.....	163
Purulent urine with positive cultures.....	150
Purulent urine with negative cultures.....	140

occurred. The reactions observed in these nine cases were sufficiently grave to require us to discontinue administration of sulfanilamide to the subjects concerned. Because all the patients were hospitalized for the duration of the experiment, it was permissible, therefore, to persevere with the drug in the face of what would constitute a contraindication to its use under less ideal conditions. Mild reactions occurred in a number of other cases but in these nine the reaction was severe enough to require withdrawal of the drug. It should be emphasized again that sulfanilamide is a

drug not without danger, especially when administered to the elderly patient. Its use as a routine urinary antiseptic in postoperative cases is to be deprecated.

The urinary infections that exist before operation or develop afterward are, in actual experience, very rarely the cause of anxiety. Certainly a stormy convalescence owing to such infections had a much lower incidence than did undesirable reactions to sulfanilamide. Actually, in the present series, there were only three patients in each of the groups in whom febrile reactions ensued that could be regarded as characterizing a mildly stormy convalescence.

CONCLUSIONS

A study of the efficacy of sulfanilamide as a urinary antiseptic in the postoperative management of 100 cases of transurethral resection has been made.

A control series of a similar number of cases was studied concurrently.

Our experience has not demonstrated a sound basis for administration of sulfanilamide in routine postoperative management of these cases. In fact, the unfavorable reactions from it may hinder convalescence.

It is our opinion that the results of its administration in other types of surgical cases wherein the drug is expected to act as a urinary antiseptic will be similar to ours. Its routine use, therefore, seems unwarranted.

THE USE OF BENZEDRINE SULFATE IN POSTENCEPHALITIC PARKINSONISM

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Benzedrine has been referred to in the literature by many chemically descriptive terms such as benzyl methyl carbinamine, alpha methyl phenylethylamine, beta phenylisopropylamine, phenylaminoethanol and beta aminopropylbenzene. We shall confine ourselves to the use of the trade name benzedrine sulfate in future reference.

Pharmacologic studies¹ have shown that benzedrine has a more profound central stimulating action on the central nervous system than either epinephrine or ephedrine. Its action has been estimated to be sustained from two to eight times as long as that of ephedrine. Its central effect is probably due to an increased cerebral blood flow and a possible chemical action on the brain itself.² Its action as a vasopressor causes the blood and spinal fluid pressures to increase.³ The use of the parasympathetic paralyzants, hyoscyamus, belladonna and stramonium enhances the sympathetic stimulating action of benzedrine, thereby increasing its pressor effects. Dameshek² has shown an increased erythrocyte count during the use of this drug. Lagen,

Soley and Leake⁴ have reported an increase in the basal metabolic rate in a small series of cases.

Extremely good results have been obtained in persons in a depressed mood, in those who are easily fatigued and in the chronically exhausted and self absorbed.⁵ Following the administration of benzedrine, an improvement of more than 8 per cent had been noted in intelligence scores.⁶ Benzedrine sulfate has proved ineffectual in catatonic stupors.⁷ Favorable results have been obtained in ameliorating the symptoms of those suffering from orthostatic hypotension.⁸ In some cases of myasthenia gravis, good results have been obtained by the use of benzedrine as a supplement to prostigmine therapy.⁹ Benzedrine has been reported to be three times as effective as ephedrine in narcolepsy and has afforded almost complete relief from cataplectic symptoms.¹⁰ In some of these cases in which ephedrine proved inactive even in large doses, benzedrine was effective in small doses.

Recently reports of small series of cases¹¹ have tended to show the effectiveness of benzedrine sulfate in postencephalitic parkinsonism. They have shown that the useful action of this drug is chiefly on the subjective symptoms, although 100 per cent of the patients suffering with oculogyric crises were relieved. Likewise in 100 per cent of the cases an increase in energy and disappearance of drowsiness was noted. The strength and muscular rigidity were also favorably affected, though to a less degree. In a disease respecting neither age nor sex, which marches so gradually and relentlessly to progressive helplessness, a drug which may stay its progress or offer some relief is worthy of trial. It was with this purpose in mind that we began this study in July 1936.

From the neurologic wards and the outpatient department of the Philadelphia General Hospital, ninety cases of parkinsonism were chosen for our study. In only seventy-four of these cases were we able to complete our observations, owing to discharges and transfers of seven ward patients and to the lack of cooperation of nine of our clinic patients. We feel satisfied that in

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