THE TREATMENT OF E. COLI URINARY INFECTIONS WITH SULFATHALIDINE (PHTHALYLSULFATHIAZOLE)[1]

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In 1944 one of us (H. S. E.) reported before the American Gynecological Society and the Baltimore City Medical Society the results of studies made with the collaboration of Roger B. Scott, resident gynecologist, and Philip P. Steptoe, resident obstetrician, upon the use of sulfasuxidine (succinylsulfathiazole) in the treatment of urinary infections. (This report was published in the *American Journal of Obstetrics and Gynecology*, January 1945.

Our conclusions from that study were that the drug in the doses given, 0.25 gm. per kilogram of body weight in 4 or 6 divided doses daily, was usually effective in the treatment of urinary infections due to E. coli, but not in those due to other types of organisms. The urine was usually sterile after the first week of treatment but continuation of the drug in doses of 0.125 gm. per kilogram of body weight daily for 2 additional weeks, it was believed gave greater protection against recurrence of infection. The drug was effective against cases previously found resistant to treatment by other sulfonamides, and was well tolerated by patients who had proved sensitive to other sulfonamides, or who because of poor renal function or severe anemia it was believed would have tolerated them poorly.

The chief and, we may say, only objection to sulfasuxidine was the large doses required to achieve the desired results. Shortly before conclusion of the studies on that drug, there was made available to us by Sharp and Dohme phthalylsulfathiazole or sulfathalidine which had been shown experimentally to be quite as efficient in reducing the count of coliform organisms in the intestinal content as sulfasuxidine, and to accomplish this purpose when administered in only one-fourth to one-third the dosage required with the latter drug. We therefore undertook to extend our studies upon E. coli urinary infections to this drug, and the results of this study we shall now report to you in full. The dose given in most cases has been 1 gm. 4 times daily over a period of 3 weeks.

Poth and Ross found that sulfathalidine rarely causes toxic manifestations and is an effective bacteriostatic agent for coliform organisms and Clostridia in the intestinal tract in doses from one-fourth to one-half those required to produce a similar effect by sulfasuxidine. In the treatment of infectious diseases of the colon, Streicher has found the optimal dose to be 3 gm. daily in divided doses. This author has kept some patients with ulcerative colitis continuously upon the drug for periods varying from 6 to 9 months without evidence of toxic or other harmful effects.

As with sulfasuxidine, the drug is poorly absorbed from the intestinal tract and regardless of the dosage, Poth and Ross and also Streicher found that the

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blood level of both the free and conjugated forms, that is sulfathiazole, acetylated sulfathiazole and phthalylsulfathiazole combined, rarely exceeded 1.5 mg. per 100 cc. The daily urinary excretion is approximately 5 per cent of the drug ingested, and this is divided about equally between the free and combined forms, ratio 0.100 gm. sulfathiazole to 0.104 gm. of phthalylsulfathiazole on a daily dosage of 0.125 gm. per kilogram of body weight.

Thus on a daily dosage of 4 gm. of the drug such as most of our patients have received, the total daily sulfonamide excretion in the urine would be 0.2 gm. or approximately 0.1 gm. each of sulfathiazole and sulfathalidine. Assuming an average daily urine output of 1500 cc the concentration of each of the two drugs in the urine would be approximately 6.6 mg. per 100 cc.

TABLE 1. *Immediate results of treatment of 50 patients with E. coli urinary infections with sulfathalidine*

TYPE OF INFECTION	NO. OF CASES	BACTERIOLOGIC CURE		SYMPTOMATIC CURE	
		No.	Per cent	No.	Per cent
Pyelitis or cystitis of pregnancy	Cystitis 1, Pyelitis 7 = 8	5	62.5	8	100
Puerpural pyelitis or cystitis	Cystitis 1, Pyelitis 6 = 7	7	100	7	100
Chronic or recurring cystitis	13	12	92	12	92*
Acute cystitis	1	1	100	1	100
Acute pyelitis	3	3	100	3	100
Chronic or recurring pyelitis	18	15	83.3	18	100
Total.....	50	43	86	49	90†

* The bacteriologic and symptomatic failure in this group was not in the same patient.

† Some of the most striking clinical and symptomatic improvements were obtained in patients whose urines were not rendered sterile.

Fifty cases with various types of urological disease and with urine infected by E. coli have been found suitable for reporting. Urines with Aerobacter aerogenes and other types of organisms commonly found in the urinary tract were never rendered sterile by the drug, and therefore patients with such infections have not been included, although some of them, especially those with Aerobacter aerogenes infection, were often greatly improved symptomatically.

In table 1 are shown the immediate results of treatment in 50 cases studied. All but one of the patients experienced great symptomatic benefit, and this was true of all of the 7 in whom the urines could not be rendered sterile. The urine of the patient who received no symptomatic relief became sterile very promptly, and it was finally concluded that this patient was suffering from relatively mild interstitial cystitis upon which an E. coli infection had been superimposed.

Of the 7 patients in whom the urine could not be rendered sterile, 4 were suffering from obstructive lesions that could not be entirely eliminated, one had cystitis and ureteritis cystica, and one a small calculus in the right pelvis considered too small to warrant operative removal. In the seventh patient no ascertainable cause for the inability to render the urine sterile could be found. This patient has proved to be one of the most interesting ones of the series and will be reported in some detail later.

Twenty-four of the patients have been followed for periods varying from 6 to 30 months since the completion of treatment, and 21 others for shorter periods,

TABLE 2. *Late results of treatment of E. coli urinary infections with sulfathalidine*

TYPE OF INFECTION	NO. FOLLOWED 6–30 MONTHS	BACTERIOLOGIC CURE		SYMPTOMATIC CURE		NO. FOLLOWED 2–6 MONTHS	BACTERIOLOGIC CURE		SYMPTOMATIC CURE	
		No.	Per cent	No.	Per cent		No.	Per cent	No.	Per cent
Pregnancy infections...	4	3	75	4	100	2	2	100	2	100
Puerpural infections...	4	4	100	4	100	1	1	100	1	100
Chronic or recurring cystitis.....	4	3	75	3	75	8	5	62.5	6	75
Acute cystitis.....	1	1	100	1	100					
Acute pyelitis.....						3	3	100	3	100
Chronic or recurring pyelitis.....	11	7	63.6	11	100	7	5	71.5	6	85.7
Total.....	24	18	75	21	87.5	21	16	76	18	85.7
Total followed both groups.....	40	34	75.5	39	86.6					

TABLE 3. *Results of a second course of sulfathalidine in seven patients who received a second course for late recurrence of infection after an immediate cure from the first course*

Months after first course that recurrence occurred.....	9	6	14	4	4	6	4
Months followed after second course..	2	3	11	failure	2	6	3

2 to 6 months. This latter group is composed of those patients who have been treated too recently to permit of longer follow up studies, and some of those suffering originally from acute infections who, once relieved of their symptoms, have been found difficult to induce to return at regular intervals for follow up cultures. The results of the follow up studies in these 45 patients are shown in table 2.

Seven patients in whom late recurrences of infection occurred were given a second course of the drug with successful eradication of the recurrent infection in all but one. In table 3 are shown the elapsed time between the first course of treatment and the recurrence, and the number of months that the urine has remained sterile since the second course in these seven patients.

One of the chief assets of this drug as well as sulfasuxidine is that it often proves effective in patients in whom other sulfonamides, chiefly sulfadiazine and sulfathiazole, have failed or have been poorly tolerated. There were 22 such patients in this group, and the results of treatment of these with sulfathalidine are shown in table 4.

TABLE 4. *Results of sulfathalidine treatment of patients with E. coli infections previously treated unsuccessfully with other sulfonamides*

TYPE OF FAILURE		TOTAL FAILURES	IMMEDIATE CURE WITH SULFATHALIDINE		LATE CURE	
			No.	Per cent	No.	Per cent
Unsuccessful	12					
Rapid recurrence	7	22	16	72.7	14	63.6
Intolerant to drug	3					

These overall results we believe indicate the value of this drug in the treatment of infections of this type. The case may be further strengthened, however, by the citing of a few individual cases:

CASE REPORTS

Case 1. M. W., aged 31, an Army nurse married to a soldier, was first seen on October 31, 1944. In 1940 while in training she had passed a small calculus and had been studied cystoscopically at that time with essentially normal findings, including sterile urine from the bladder and both kidneys. The trouble for which she consulted us had begun in October 1943 while she and her husband were both stationed in the Hawaiian Islands. At this time she suffered an attack of acute pyelitis and cystitis which was relieved promptly by sulfonamide therapy. Very soon after this, the middle of November 1943, she became pregnant. In January 1944 there was a recurrence of pyelitis and cystitis, and although the organism was reported as E. coli she was treated with penicillin. She improved and was transferred from Hawaii to the Letterman General Hospital where she aborted 10 days after arrival. From that time until she consulted us, she had been under observation and treatment in several Army hospitals with persistent pyuria and E. coli bacilluria in spite of repeated cystoscopic and varied chemotherapeutic treatments. Secondary anemia and leucopenia had developed, and for this reason she considered herself intolerant to sulfonamides. She was suffering from backache when on her feet, pains in the lower abdominal quadrants, and frequent attacks of bladder spasm after voiding. She was psychically depressed as a result of the abortion and the subsequent long illness.

She was referred to a medical colleague, Dr. Vernon Norwood, for study of the blood picture and general upbuilding regime. He found the blood picture essentially normal except for a moderate leucopenia, white count 4,000.

On November 20 she was hospitalized and complete cystoscopic studies carried out. The pyelograms were essentially normal on both sides, and 25 per cent of phenolsulphonphthalein was excreted by each kidney in a half hour. Cultures

from the bladder and both kidneys, however, showed heavy growths of E. coli. Under Dr. Norwood's treatment the white count had risen to 5,500, and a course of sulfathalidine, 4 gm. per day, was started and continued for 3 weeks. This produced no ill effect upon the blood picture or otherwise and resulted in great symptomatic improvement, but the bladder cultures remained positive. She was discharged from the Army in January and seen frequently throughout the winter and spring by Dr. Norwood and myself. From March 10 to March 20, he again tried sulfadiazine, 2 gm. daily, because of slight increase in the urinary symptoms, but the cultures remained positive. On June 8, the hemoglobin was 85 per cent and the white count 6,000, the urine was grossly clear and microscopically negative, but still showed E. coli on culture. She felt quite well and as her husband was at home on furlough insisted on attempting another pregnancy, although we advised strongly against it.

She was not seen again until August 31, when she came in looking well and feeling well except for moderate nausea of pregnancy, her last menstrual period having been June 18. The urine, however, showed 8 to 10 white blood cells per high power field and a heavy growth of E. coli. Sulfadiazine 2 gm. daily was again given for a week, but on September 11 and October 15 cultures were still positive for E. coli.

On November 1, 1945 symptoms of acute pyelitis developed. She was started on sulfathalidine, 4 gm. daily, at once, and this was continued throughout the remainder of her pregnancy and puerperum. The acute symptoms subsided within 2 days and never recurred, but cultures taken at each obstetrical visit showed E. coli consistently, and occasionally various types of cocci which were rarely the same in two successive cultures and probably were contaminants. She underwent a normal delivery at term on April 2, 1946. At this time the white count and hemoglobin were normal and the puerperum was uneventful.

She was last seen on May 17, psychologically happy and physically well, though the urine culture still showed E. coli.

Comment: In spite of the fact that this case was a failure bacteriologically speaking, we consider it one of the triumphs of the drug. When the patient first consulted us she was well on the way to physical and psychological invalidism. She now has a healthy baby and considers herself healthy. Had it not been for the treatment with sulfathalidine it is highly probable that her second pregnancy might of necessity have been terminated prematurely with disastrous psychic result to the patient.

Case 2. C. A., white, was first seen in 1936 at the age of 17 for evaluation of the status of the urinary tract because of a history of pyelitis in infancy. Intravenous pyelograms at that time showed normal upper urinary tracts, but the bladder urine showed a few white blood cells and red blood cells and E. coli on culture. In December 1938 she suffered from pyelitis of pregnancy at the fifth month of gestation. She was admitted to the obstetrical service and treated with sulfanilamide with symptomatic improvement and clearing of pus from the urine, but with cultures remaining persistently positive for E. coli. A normal delivery at term on April 27, 1939 was followed by a febrile puerperium with

pain in the right flank and pus and E. coli in the urine. Sulfonilamide again relieved the symptoms but failed to sterilize the urine. Intravenous pyelograms made on September 28, 1939 showed bilateral hydroureteronephrosis, more marked on the right side, and from November 11 to 17, 1939 she was given a third course of sulfonilamide, again without success in sterilizing the urine.

Subsequent to this in November 1939 complete cystoscopic studies were done which revealed a half hour phenolsulphonphthalein excretion of 10 per cent by the right and 30 per cent by the left kidney. Cultures were positive for E. coli from the bladder and both kidneys. Retrograde pyelogram of the right tract showed blunting of the calyces, with slight narrowing of the ureteropelvic junction, and some dilatation of the ureter below this point. The left pyelogram showed similar findings. She was treated by ureteral dilatations during 1940, and in March 1942 the differential phenolsulphonphthalein was essentially normal, but cultures were still positive for E. coli from the bladder and right kidney. Reevaluation in August 1945 showed similar findings except that the only pyelographic abnormality was a moderate dilatation of the right ureter.

Sulfathalidine, 4 gm. daily, was given for 3 weeks beginning September 17, 1945. The bladder urine was sterile on October 6, and remained sterile in 5 subsequent cultures until April 2, 1946 when it again showed E. coli. A culture on July 27 again showed E. coli and a second course of sulfathalidine was begun on August 29. Subsequent cultures have all been sterile.

Comment: The patients's infection has produced very few symptoms except during her pregnancy and puerperium. Her chief interest has been in the advisability of another pregnancy. For a long time we believed that this was inadvisable. Now, however, in view of the facts that we have been able twice to sterilize the urine with sulfathalidine, and that her renal function is normal, we believe that another pregnancy may be safely undertaken. Even should urinary infection occur during the pregnancy, we believe that it could be safely controlled as in case 1.

Case 3. A. M., white, aged 22 was seen first February 10, 1938, at the seventh month of her first pregnancy, having had symptoms of right pyelitis since late December. She had been treated ineffectively with sulfathiazole, which had been tolerated poorly and had caused severe nausea and vomiting. She was running low-grade fever, and the urine contained much pus and showed a heavy growth of E. coli. Strangely, she tolerated ammonium mandelate well and was kept afebrile until term by almost continuous use of this drug. The cultures remained positive, however, and whenever the drug was omitted the fever recurred.

After delivery the fever and symptoms subsided. On April 3, 1939, appendectomy was performed for acute appendicitis. Intravenous pyelograms made during the convalescence showed normal kidneys and ureters. The bladder culture showed E. coli but the kidney cultures were sterile. Ammonium mandelate was again given, and bladder cultures obtained on June 12 and August 14, were sterile.

A second pregnancy was uncomplicated, and the patient was delivered in

November 1941. She was seen next on January 16, 1943, four and a half months pregnant, with symptoms of mild acute right pyelitis. The urine contained pus and the cultures showed E. coli. On January 22, six days after beginning sulfasuxidine, there were no symptoms, and the urine was negative microscopically and on culture. There were no further complications during the pregnancy, but when the patient returned by request on February 28, 1944, the urine showed E. coli bacilluria but only an occasional pus cell. Treatment with sulfathalidine, 0.1 gm. per kilogram daily, was instituted and cultures obtained on March 13 and 27, May 29 and October 3, 1944 were sterile. There was recurrence of mild urinary symptoms intermittently during the winter and spring of 1945. These were associated with respiratory infections for which a tonsillectomy was done. On May 7 the urine culture showed paracolon bacilli and sulfathalidine was repeated. There have been no subsequent urinary symptoms and cultures remained sterile through April 1946, the last one taken.

Comment: This patient again illustrates the value of these drugs in the treatment of pyelitis associated with both the pregnant and nonpregnant states. She further illustrates the complete toleration of both of the drugs by a patient who could not take sulfathiazole.

DISCUSSION

We can only speculate as to the mode of action of these drugs in accomplishing the results set forth. Alyea, Cook, and others have shown that large doses and high urine concentrations of the sulfonamide drugs are not necessary in the treatment of urinary infections, and the average daily dose of sulfathiazole or sulfadiazine suggested by these authors is 1.5 to 2 gm. It might be argued from this that even the small amount of free sulfathiazole present in the blood and urine as a result of administration of sulfasuxidine or sulfathalidine may be the active agent in rendering the urine sterile. This argument seems untenable, however, in view of the very small amounts of sulfathiazole found in the blood and urine, and in view of the fact that several patients were successfully treated with these drugs, whose infections had failed to respond to relatively large doses of sulfathiazole.

A more likely possibility it would seem is that the drugs themselves, sulfasuxidine and sulfathalidine, even in the low concentration in which they appear in the blood and urine may exert a stronger bacteriostatic and bacteriocidal effect upon E. coli than is exerted by sulfathiazole and sulfadiazine even in considerably greater concentration.

The only other alternative would seem to be that the tissues of the urinary tract are given an opportunity to rid themselves of the existing infection because the constant source of infection in the bowel is temporarily eliminated.

The reason for persistence of cure, in at least some of those patients who had previously exhibited chronicity or rapid recurrence of infection in spite of other forms of sulfonamide therapy, seems even more difficult to explain. Three possible explanations may be suggested:

First, elimination of the source of infection from the bowel for a period of 3

weeks may give the tissues of the urinary tract time to recover sufficient natural resistance to infection to protect them against recurrence.

Second, the beneficial effect exerted by the drug upon the intestinal tract may decrease the avenues for escape of organisms into the blood stream or lymphatic channels through which they may have been reaching the urinary tract.

Third, there may be certain strains of E. coli with a selective affinity for the urinary tract which are completely and permanently eradicated as a result of administration of the drugs.

It seems probable that either the first or second of these mechanisms, or perhaps both of them, may be the explanation for the persistence of cure. It is for this reason that it has been considered advisable to continue the drug for at least 2 and preferably 3 weeks. In the majority of those patients cured, the cultures became sterile in less than a week after administration of the drug was begun, so that such an extended course was not necessary to effect an immediate cure.

As regards the third possibility, Meisser and Bumpus long ago demonstrated a selective affinity for the urinary tract upon the part of certain strains of streptococci. In 1917, Helmholz and Beeler reported a chance finding which suggested that there may be a similar selective affinity among strains of colon bacilli. Injecting intravenously into rabbits strains of B. coli isolated from the urine of children suffering from pyelocystitis, these authors produced renal lesions in only 8, or 12 per cent, of 66 animals, and the tendency of the organisms to produce lesions in other organs was just as great as in the kidney. In similar experiments using a strain of B. coli communior isolated from the urine of a rabbit with a severe spontaneous urinary infection, pyelonephritis was produced in 22, or 70 per cent, of 32 rabbits, and only 3 of these showed lesions outside the urinary tracts. No other similar contributions have been found in the literature, however, and from discussion of the problem with several expert bacteriologists we have gained the impression that little is known of specificity of strains of the colon flora, and that any attempt to settle this question experimentally would be met with insurmountable difficulties.

CONCLUSIONS

Sulfathalidine has been found effective in the treatment of urinary infections due to E. coli.

Administration of the drug in appropriate dosage, approximately 0.1 gm. per kilogram of body weight daily, usually renders the urine sterile by the end of 1 week.

Continuation of the drug for 2 additional weeks, we believe, furnishes greater protection against recurrence of infection.

The drug has proved effective against infections which had proved resistant to other sulfonamides.

It is not effective bacteriologically against organisms other than E. coli.

It is tolerated well by patients who have reacted badly to other sulfonamides, and by patients with anemia, leucopenia, or low renal function who ordinarily tolerate other sulfonamides poorly.

Sulfathalidine has been administered to at least 1 patient throughout 5 months of pregnancy without demonstrable harmful effects.

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REFERENCES

ALYEA, E. P.: Sulfathiazole therapy in urinary tract infections. J. Urol., **47:** 219, 1942.

COOK, E. N.: Chemotherapy in urology. J. A. M. A., **115:** 2079, 1940.

EVERETT, H. S., SCOTT, R. B. AND STEPTOE, P. P., JR.: The treatment of urinary infections with sulfasuxidine (succinylsulfathiazole). Am. J. Obst. and Gynec., **49:** 114–127, 1945.

HELMHOLZ, H. F. AND BEELER, C.: Focal lesions produced in the rabbit by colon bacillus isolated from pyelocystitis cases. Am. J. Dis. Child., **14:** 5, 1917.

MEISSER, J. G. AND BUMPUS, H. C.: Focal infection and selective localization of streptococci in pyelonephritis. Arch. Int. Med., **27:** 326, 1921.

POTH, E. J. AND ROSS, C. A.: The clinical use of phthalylsulfathiazole. J. Lab. and Clin. Med., **29:** 785, 1944.

STREICHER, M. H.: Phthalylsulfathiazole ("sulfathalidine"), clinical, chemical and bacteriologic evaluations in infectious diseases of the colon. J. A. M. A., **129:** 1080, 1945.