to the possible dangers of producing hypopotassemia, he and later Bywaters and Joekes,[11] both recommended that physiological amounts of potassium be included in the dialysing fluid.

From Kolff's[7] data it was apparent that hypopotassemia occurred only in a patient who had a normal serum potassium concentration to start with, very similar to that in case III, Table I.

The variable results obtained in these cases are probably due to the differences in the direction of the potassium shift. In case II, the increase of 7.6 g of potassium in the dialysing fluid during the dialysis indicated that potassium was removed from the intracellular as well as from the extracellular fluids. In cases I and III, since there was no significant increase of potassium in the dialysing fluid, the potassium shift probably occurred mainly from the extracellular to the intracellular fluids. The lowering of the serum potassium in these instances might be explained by other factors: (a) the dilution of the patient's blood with the blood added to the artificial kidney prior to its use, and by the further addition of varying amounts of blood and intravenous fluids during the treatment: (b) the fact that the glucose present in very high amount[7,11] in the blood leaving the artificial kidney to be returned to the body will, on entering the systemic circulation, be stored as glycogen, with the resultant shift of potassium from the extracellular to the intracellular spaces[10] was the main reason that Bywaters and Joekes[11] recommended that physiological amounts of potassium to be added to the dialysing fluid; and (c) potassium elimination from the blood stream by urinary excretion. This last factor may have operated in Case III where the patient voided 1,200 cc urine during the period of dialysis.

Summary. From the observations reported it would appear that the artificial kidney can serve as a safe and efficient method for removing excess potassium from the body in uremia patients with hyperpotassemia. However, further study is required to determine the amount of potassium that should be added to the dialysing fluid in each individual case. This will probably vary with the degree of hyperpotassemia present before treatment is begun.

We wish to express our thanks to Doctors G. G. Miller and J. T. MacLean for permission to study their patients. We are grateful to Dr. Martin Hoffmon for many helpful suggestions and criticisms.

11 Bywaters, E. G. L., and Joekes, A. M., *Proc. Royal Soc. Med.*, 1948, **41**, 420.

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17065. Nu 445 in the Treatment of Urinary Infections Due to Gram Negative Bacilli.*

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Introduction. Nu 445† (3,4-dimethyl-5-sulfanilamido-isoxasole) is one of the newer sulfonamides said to be highly effective for urinary tract infections due to *E. coli* and *B. proteus.*[1-6] The reported results on the therapeutic activity of this drug in man are meager

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1 Schnitzer, R. J., Foster, H. K., Ercoli, N., Soo-Hoo, A., Mangieri, C. N., Roe, M. D., *J. Pharm. and Exp. Therap.*, 1946, **88**, 47.

2 Sarnoff, S. J., PROC. SOC. EXP. BIOL. AND MED., 1948, **68**, 23.

3 Narins, L., *J. Urol.*, 1948, **59**, 92.

4 Sarnoff, S. J., Freedman, M. A., Hyman, A. A., *J. Urol.*, 1946, **55**, 417.

TABLE I.
Comparative *in vitro* Sensitivity of Several Strains of Various Gram Negative Micro-organisms to 4 Sulfonamides.

Strain	Nu 445‡ titers in mg %		ST‡ titers in mg %		SD‡ titers in mg %		SMT‡ titers in mg %	
	c*	st†	c	st	c	st	c	st
E. coli 1	750	500	500	100	250	50	25	25
" 2	1000	500	500	100	250	100	250	100
" 3	750	500	1000	1000	1000	250	50	25
" 4	100	25	500	250	500	250	750	100
" 5	250	100	500	100	500	25	500	250
A. aerogenes 1	750	500	500	100	>1000	>1000	750	500
" 2	>1000	>1000	1000	750	>1000	1000	250	100
" 3	>1000	>1000	>1000	>1000	>1000	>1000	>1000	>1000
" 4	1000	500	500	100	>1000	1000	750	500
B. proteus 1	>1000	500	750	50	250	25	100	25
" 2	>1000	>1000	1000	500	>1000	>1000	500	100
" 3	>1000	>1000	>1000	>1000	>1000	>1000	1000	750
" 4	250	100	1000	500	>1000	>1000	750	250
B. pyocyaneus 1	>1000	>1000	>1000	1000	>1000	>1000	750	500
" 2	500	100	>1000	750	>1000	>1000	1000	500
" 3	>1000	>1000	500	100	>1000	>1000	750	500
" 4	>1000	1000	>1000	>1000	>1000	>1000	500	100
E. typhi 1	1000	250	500	250	1000	500	250	50
" 2	750	250	500	100	1000	500	500	100
S. paratyphi 1	1000	250	500	250	>1000	>1000	250	25
" 2	1000	250	750	500	>1000	>1000	250	100
S. schottmuelleri 1	>1000	1000	>1000	750	>1000	>1000	500	100
" 2	>1000	1000	>1000	750	>1000	750	500	100

* c = bactericidal titer.
† st = bacteriostatic titer.
‡ NU 445—3,4-dimethyl-5-sulfanilamido-isoxasole.
ST —sulfathiazole.
SD —sulfadiazine.
SMT —sulfamethazine.

and conflicting. *In vitro* and *in vivo* studies on animals showed that sulfadiazine was slightly superior to Nu 445 against *E. coli,* moderately superior against *S. schottmuelleri* and greatly superior against *Klebsiella A.*[1] Because of these inconsistencies, a further clinical and *in vitro* study of the drug is herewith reported.

In vitro studies: The *in vitro* action of the drug on various gram negative bacilli was determined and compared with that of sulfadiazine (SD), sulfamethazine (SMT), and sulfathiazole (ST).

Serial dilutions of a 1% solution of the drug in nutrient broth (pH 8.2) were made, and to 0.9 cc of each dilution was added 0.1 cc (500 to 3000 microorganisms) of a bacterial suspension from a 24-hour growth. The highest drug dilution at which there was no macroscopically visible growth after 24 hours at 37° was taken to be the bactericidal titer (c). The highest drug dilution in which there was definitely less turbidity as compared to the control tubes was taken to be the bacteriostatic titer (st).

Most of the bacterial strains tested were freshly isolated from infected urines. *E. typhi* and the *Salmonellae* had been cultured from stools or blood and had undergone a number of transfers.

Table I shows that the 4 sulfonamides test-

[5] Rodgers, R. S., Colby, F. H., *J. Urol.*, 1948, **59**, 659.

[6] Haines, W. H., Micelli, S., *Penn. Med. J.*, 1947, **50**, 1328.

TABLE II.
Results of Treatment with Nu 445 in Uncomplicated* and Complicated† Urinary Infections.

Type of disease	Type of infection	No. of cases	Cases cured, No.	Cases not cured, No.
Uncomplicated	Monovalent	7	6	3
	Polyvalent	2		
Complicated	Monovalent	1	1	10
	Polyvalent	10		
Total		20	7	13

* Uncomplicated means acute cystitis, acute pyelitis, or acute pyelonephritis without any additional pathology.

† Complicated means additional pathology such as severe chronic infection, calculi, hydronephrosis, obstruction to urinary flow, or constant drainage.

ed exert differing effects on various strains of the same species of bacteria. For example, of the 5 *E. coli* strains tested, 2 were most sensitive to SMT, 2 to Nu 445, and one equally to SD and SMT. Of 4 strains of *Ps. aeruginosa, (B. pyocyaneus),* 3 were best inhibited by SMT, one by Nu 445. The effect of SMT on the typhoid-paratyphoid group was definitely superior to that of the other 3 drugs. From the foregoing data, Nu 445 appeared to be worthy of clinical trial in infections due to *E. coli, B. proteus,* or *Ps. aeruginosa.*

Clinical Observations. Twenty unselected patients with a variety of urinary tract infections due to gram negative bacilli were given Nu 445 orally. In spite of large daily doses, the blood levels remained rather low indicating rapid acetylation and excretion of the drug.[5]

The results of treatment are indicated by 2 types of response. A. Clinical and bacteriological cure. This result was obtained in 7 patients (35%). The patients in this group were followed for at least 2 weeks, and at least 2 sterile cultures were obtained after termination of treatment. B. Clinical and bacteriological failure. Of the 13 patients (65%) in this group, 3 showed temporary improvement, but had a recurrence shortly after the drug was omitted.

Discussion. The results of treatment with Nu 445 are inferior to those obtained with SMT and other sulfonamides.[7-12] Six of 7 patients with pure *E. coli* infection and one patient with pure *B. proteus* infection were cured. Four of these had received SD without benefit. Not one of 12 patients with mixed infection was cured. Three, however, for various reasons, did not receive a full course of the drug. Ten of the 12 had complicating pathology such as obstruction, calculi, hydronephrosis or constant drainage, etc. (Table II).

Although alkali therapy was not administered, the urine pH ranged from 4.5-7.5. No renal damage or crystalluria was observed in any patient. In 2 patients a dose of 12 g daily for several days and in one patient a dose of 19 g inadvertently given in one day, did not produce any toxic symptoms. Mild nausea and vomiting occurred once after 6 g had been given daily for 4 days, and disappeared within 24 hours after termination of therapy.

Nu 445 is a safe and effective drug in uncomplicated monovalent infections of the urinary tract due to *B. proteus* or *E. coli,* but is of little or no value in polyvalent infections, and in those associated with complicating organic disease in which SD[8] and SMT[7] have occasionally achieved cure. However, Nu 445, like other sulfonamides and antibiotics, may produce a cure when other drugs do not.

Summary. 1. An *in vitro* study of the action of Nu 445 shows that this drug occasionally

[7] Rutenburg, A. M., Schweinburg, F. B., *Surgery,* 1949.

[8] LaTowsky, L. W., *J. Urol.,* 1943, **50**, 623.

[9] Satterthwaite, R. W., Hill, J. H., and Young, H. H., *J. Urol.,* 1941, **46**, 101.

[10] Helmholz, H. F., *Proc. Staff Meetings, Mayo Clinic,* 1942, **17**, 529.

[11] Culp, O. S., *J. Urol.,* 1940, **44**, 116.

[12] Alyea, E. P., *J. Urol.,* 1942, **47**, 219.

exerts a greater bacteriostatic and bactericidal effect on certain strains of gram negative bacilli than do other sulfonamides.

2. Clinical trial in 20 patients with urinary infections indicated excellent effectiveness of the drug in uncomplicated, monovalent infections due to *E. coli* or *B. proteus*.

3. Results of treatment in polyvalent infections and in cases with complicating pathology were poor.

4. The marked lack of toxicity of Nu 445 recommends its use in appropriate cases, in which it will occasionally be found to be more effective than other sulfonamides.

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17066. Metabolic Fate of 4,4'-Diaminodiphenylsulfone (DDS) in the Rabbit and its Isolation from Urine.

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4,4'-Diaminodiphenylsulfone (DDS) and many of its derivatives have been used with a measure of success in the treatment of experimental tuberculosis.[1,2] More recently the potentiating action of some sulfone derivatives on streptomycin has also been shown.[3] Of the various types of sulfone derivatives indirect evidence has indicated that certain disubstituted derivatives like promin, diasone and possibly sulphetrone are metabolized to the toxic parent substance DDS while the monosubstituted alkyl and hydroxyalkyl derivatives do not appear to undergo such transformation in the body to an appreciable extent.[4] Indirect evidence has also indicated that DDS itself does not change to any significant degree in the body, at least in so far as acetylation is concerned.[1,5] Obviously, direct evidence on these points can only be had by the actual isolation of DDS from the urine. The present report describes a satisfactory method for the isolation and recovery of DDS added to rabbit urine and the isolation and the identification as DDS of about 70% of the total diazotizable material in the urine of rabbits given DDS orally.

Procedure. The isolation of DDS from rabbit urine is based on the solubility of its hydrochloride in water and the relative insolubility of the base in water, but its ready solubility in ethyl acetate. Ethyl acetate appears to be the most satisfactory of several water-immiscible solvents tried.

The urine is made strongly alkaline to litmus with NaOH and chilled on ice for a while to aid precipitation of the base. It is then shaken out thoroughly 2 to 3 times in a separatory funnel with 30 to 50 cc of ethyl acetate, allowing as complete separation as possible each time. The partly emulsified combined ethyl acetate extract is cleared by the gradual addition of anhydrous sodium sulfate with stirring. The clear ethyl acetate solution is decanted and the Na_2SO_4 residue is washed 2 to 3 times with small portions of ethyl acetate.

The combined ethyl acetate extracts are washed once with about 5 cc H_2O and then thoroughly extracted with 5 cc portions of N HCl. This should be repeated 5 to 7 times. The combined acid extract is chilled on ice

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2 Smith, M. I., *N. Y. State J. Med.*, 1945, **45**, 1665.

3 Smith, M. I., McClosky, W. T., Jackson, E. L., and Bauer, H., PROC. SOC. EXP. BIOL. AND MED., 1947, **64**, 261.

4 Smith, M. I., Jackson, E. L., Junge, J. M., and Bhattacharya, B. K., *Am. Rev. Tuberc.*, in press.

5 Smith, M. I., and McClosky, W. T., *Am. Rev. Tuberc.*, 1945, **52**, 304.