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Aureomycin in Urinary Infections Due to Gram Negative Organisms.*

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(Introduced by J. Fine.)

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Aureomycin hydrochloride ("Duomycin")† has been reported to be a non-toxic antibiotic effective against a variety of gram-positive and gram-negative bacteria, rickettsiae and several of the larger viruses.[1-4]

This report deals with the results of aureomycin therapy in urinary tract infections due to gram-negative bacilli in 10 patients, 9 of whom did not respond to sulfonamides, penicillin or streptomycin.

In vitro studies. Data on the *in vitro* sensitivity to aureomycin of bacteria commonly encountered in urinary infections were obtained prior to the clinical study.

Serial dilutions of aureomycin in sterile broth (pH 6.8) were prepared in concentrations ranging from 200 - 0.0125 μg/ml. To 0.9 ml of each dilution 0.1 ml of a diluted 24 hour growth, containing 1500-25,000 organisms of the strain to be tested, was added. A control tube containing the same number of bacteria in 1.0 ml of sterile broth was also prepared. The tubes were incubated for 24 hours and then examined for bacterial growth. Ten strains each of *Pseudomonas aeruginosa* (*B. pyocyaneus*), *Bacillus proteus vulgaris*, *Aerobacter aerogenes*, and *Escherichia coli* were tested for aureomycin sensitivity in this manner. All strains were isolated from infected urines and had undergone only 1-3 passages. The results, listed in Table I, indicate the lowest bactericidal and bacteriostatic titers of aureomycin. The bacteriocidal titer was taken to be the lowest concentration which completely inhibited macroscopically visible growth. The bacteriostatic titer was taken to be the lowest concentration which caused less growth than in the control tube.

The results, only half of which are listed, show that different strains of a given species of gram-negative bacteria have a wide range of sensitivity. Thus, the bactericidal titer of *Ps. aeruginosa* varies from >200 μg to 0.4 μg; of *B. proteus* from 50 μg to <0.0125 μg; of *A. aerogenes* from >200 μg to 0.05 μg; and of *E. coli* from 25 μg to 0.1 μg. *Ps. aeruginosa* and *B. proteus* have been reported[1,4] to require very high concentrations of aureomycin (100-250 μg/ml). We found this to be true of some strains, but not of others. The bacteriostatic titers for a given strain of *Ps. aeruginosa*, *B. proteus* and *A. aerogenes* were identical in most instances with the bactericidal titer; but for *E. coli* a marked difference in the two titers was the rule. The bactericidal titer of most strains of all bacteria tested varied from 1.0 μg to 0.0125 μg, indicating a high degree of sensitivity. The bactericidal titer was always the same for a given strain tested with different lots of aureomycin.

Clinical Observations. Ten consecutive patients with a variety of urinary tract infections were treated with aureomycin. Prior therapy with sulfonamides in 7, with penicillin in 6, and with streptomycin in 2 had failed to yield any therapeutic effect. In all instances the infecting bacteria had been tested and found to be resistant *in vitro* to strepto-

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† An antibiotic isolated from *Streptomyces aureofaciens* and supplied by Lederle Laboratories Division, American Cyanamid Co.

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TABLE I.
Sensitivity of Gram Negative Bacilli to Aureomycin *in vitro*.

Strain	No. of bacteria, × 1000	Bactericidal titer, in μg/ml	Bacteriostatic titer, in μg/ml
Ps. aeruginosa 1	20	>200	>200
" " 2	18	100	100
" " 3	20	50	50
" " 4	15	12.5	12.5
" " 5	25	3.2	3.2
" " 6	25	0.8	0.8
" " 7	18	0.4	0.4
B. proteus 1	2.5	50	50
" " 2	1.5	25	12.5
" " 3	3	6.25	6.25
" " 4	4	0.05	0.05
" " 5	1.5	0.025	<0.012
" " 6	1.5	<0.012	<0.012
A. aerogenes 1	2	>200	>200
" " 2	2.5	100	100
" " 3	2	3.2	3.2
" " 4	2.5	0.4	0.4
" " 5	2	0.05	0.05
E. coli 1	4	25	6.25
" " 2	5	6.25	3.2
" " 3	6	1.0	1.0
" " 4	5	0.1	0.1

mycin, penicillin, and the sulfonamides.

Four patients had univalent and 6 polyvalent infections. All patients had pyuria and the usual clinical signs and symptoms.

Aureomycin was given intramuscularly to 9 patients. The dose usually was 80 mg every 8 hours for 5-6 days, but acutely ill patients received an initial intravenous dose of 300 mg in 500 cc of saline. The tenth patient received aureomycin orally, 4 g the first day, 3 g the second day and 2 g daily thereafter, in divided doses. The duration of treatment in all cases was based on the clinical and bacteriological response. No toxic reactions were encountered. The intramuscular injections were painful. The pain was partly or wholly alleviated by dissolving the drug in 1% procaine. Table II lists the clinical diagnosis, the bacteriological findings before and after aureomycin therapy, *in vitro* sensitivity tests of the bacteria involved to various antibiotics, and the therapy given prior to aureomycin.

The results were evaluated on a clinical and a bacteriological basis. The clinical symptoms cleared up in all patients. In 3 of the 4 patients with univalent infections and in 5 of the 6 patients with polyvalent infections the urine became sterile and remained so during the 7-10 days after the drug was discontinued. In one case (No. 3), the urine was not completely sterilized, but the plate count showed a marked reduction in the number of colonies of the responsible bacillus (*A. aerogenes*). This strain, tested *in vitro* for sensitivity, was resistant to sulfathiazole, sulfadiazine, sulfamethazine, penicillin, and streptomycin. The bactericidal titer with aureomycin was higher than 200 μg. In the second case, (No. 6), one of the 2 infecting organisms, *Ps. aeruginosa,* was eliminated, while the plate count of the other, *A. aerogenes,* was markedly reduced. This latter strain was also resistant *in vitro* to the 3 sulfonamides, penicillin and streptomycin. The bactericidal titer with aureomycin was again higher than 200 μg.

Of the 20 strains of bacteria found in the 10 patients, all strains of *E. coli* (4), of *Ps. aeruginosa* (4), of *B. proteus* (2), of *Strep. viridans* (2), of *Strep. fecalis* (1), and 5 of the 7 strains of *A. aerogenes* were cleared from the urine. The two strains of *A. aerogenes* which persisted showed a high resis-

TABLE II.
The Data of Ten Patients with Urinary Infections Successfully Treated with Aureomycin.

Case No.	Diagnosis	Urine cultures before aureomycin	Growth inhibiting concentration *in vitro* of aureomycin, μg/ml	Urine cultures after aureomycin	Sensitivity tests *in vitro* with other antibiotics*	Chemotherapy prior to aureomycin	Aureomycin Daily Dose (mg)	Aureomycin Days
1	Chronic pyelonephritis, renal insufficiency	*A. aerogenes* *E. coli* *Strep. viridans*	6.25 3.2 0.8	Sterile	All 3 strains resistant to SD, ST, SMT, P and S.	None	240	6
2	Chronic pyelonephritis, ectopic kidney	*E. coli* *B. proteus*	0.05 12.5	"	Both strains resistant to P, S, SD, and SMT. *Proteus* also to ST. *Coli* moderately sensitive to ST	SD	240	5
3	Chronic pyelonephritis	*A. aerogenes* heavy growth	>200	*A. aerogenes* 1-4 colonies	Strain resistant to P, S, SD, ST, SMT	Penicillin Streptomycin	80	8
4	Pyelonephritis following prostatectomy	*B. pyocyaneus* *Strep. fecalis*	50	Sterile	*B. pyocyaneus* resistant to SD, ST, SMT, P, and S.	Penicillin SD	120	6
5	Same	*E. coli* *A. aerogenes* *B. pyocyaneus* *B. proteus* *Strep. viridans*	25 200 0.25 0.25	"	*Coli, aerogenes, pyocyaneus,* and *proteus* resistant to P, SD, ST, SMT. *Coli* and *aerogenes* slightly sensitive to S. *Proteus* and *pyocyaneus* resistant to S.	Penicillin SD SMT	160	10
6	Same	*A. aerogenes* *B. pyocyaneus*	>200 1.6	*A. aerogenes* 3-6 colonies	Both strains resistant to P, S, SD, SMT. *B. pyocyaneus* resistant to ST. *A. aerogenes* sensitive to ST.	SD Penicillin	160–240	15
7	Chronic cystitis	*E. coli* *A. aerogenes*	0.2 0.2	Sterile	Both strains resistant to P, S, SD, SMT. Moderately sensitive to ST.	Penicillin Streptomycin	60	12
8	Acute pyelonephritis and cystitis due to renal calculi	*A. aerogenes* heavy growth	0.2	"	Strain resistant to P, S, SD, SMT, ST.	SD Penicillin	240	5
9	Acute pyelonephritis and cystitis due to renal calculi	*B. pyocyaneus* heavy growth	12.5	"	*B. pyocyaneus* resistant to P, S, SD, SMT, ST.	SD Penicillin	240 2000†	4 3
10	Acute postoperative cystitis	*A. aerogenes* heavy growth	0.0125	"	*A. aerogenes* resistant to P, S, SD, ST, SMT.	SMT	2000–† 4000	6

* SD—Sulfadiazine. ST—Sulfathiazole. SMT—Sulfamethazine. S—Streptomycin. P— Penicillin.
† Oral administration.

tance to the drug *in vitro*, but were nevertheless reduced in number. Strains of *Ps. aeruginosa* and *B. proteus* which are sensitive *in vitro* to aureomycin can be eliminated from urine infected with these organisms. In all patients who were cured treatment was continued for 2 or 3 days after the urine was first found to be sterile, because in one patient not listed, on whom the drug was discontinued as soon as the urine became sterile, recurrence took place within 2 days.

Summary. 1. Aureomycin is highly effective against many strains of gram-negative bacilli *in vitro*, including many which were found to be resistant to sulfonamides, penicillin, and streptomycin. The sensitivity of various strains of a given species, however, varies greatly.

2. Clinical trial in 10 patients with urinary infections which were refractory to previous treatment with other antibiotics, resulted in a clinical cure of all ten patients. Bacteriologically eight patients were cured, and 2 were markedly improved.

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Effects of a Quaternary Amine* Capable of Blocking Functions of the Autonomic Nervous System.

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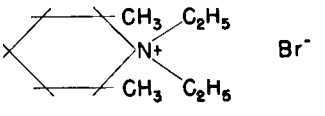
Much interest has been directed in recent years to functions of the autonomic nervous system, and to effects of drugs which interfere with activation of adrenergic or cholinergic end organs or with cholinergic synaptic transmission in autonomic ganglia. Acheson and Moe[1] and Lyons[2] have reported effects of the tetraethylammonium ion (TEABr) in the experimental animal and in man, and have shown that it blocks cholinergic transmission at autonomic ganglia and does not prevent activation of adrenergic end organs.

2, 6 dimethyl diethyl piperidinium bromide (SC 1950), a quaternary amine (Fig. 1), has been synthesized and studied by I. C. Winter and associates.[3] They found that this drug was 7 times as potent as TEABr in blocking transmission through the superior cervical ganglion of the cat and 5 times as potent as TEABr in producing block of transmission through the ganglion of the pelvic nerve which supplies the urinary bladder of the dog. It had little spasmolytic action on excised intestine, but in anesthetized and unanesthetized dogs following a preliminary contraction it generally reduced intestinal tone and contractility. Intravenous injection in anesthetized dogs produced a decrease of blood pressure. They also noted that large doses (20-25 mg/kg) in unanesthetized animals produced a flaccid paralysis and respiratory death resembling that caused by curare.

Experiments were undertaken to investigate effects of this drug upon the circula-



2,6 dimethyl diethyl piperidinium bromide

FIG. 1.

* Drug number SC 1950 furnished by the Research Laboratories of G. D. Searle and Co. Aided by a grant from G. D. Searle and Co.

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3 Personal communication from Dr. I. C. Winter of the Research Laboratories of G. D. Searle and Company.