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## Comparative values of present day urinary antiseptics

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THE COMPARATIVE VALUES OF PRESENT DAY  
URINARY ANTISEPTICS

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SENIOR THESIS

APRIL 15, 1932

JOHN C. SHARPE

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## INTRODUCTION

An infection of the urinary tract is a problem we have had with us always, so from the earliest days of empirical therapeutics, up to and through the present era of relatively scientific medicine, there has been a search for and a hope of finding some drug which will produce sterilization of the urinary tract.(1). Drugs and therapeutic measures may be attempted by oral administration, intravenous therapy, and instillation into some portion of the urinary tract directly - the kidney pelvis, the ureters the bladder, or the urethra.(2).

It will greatly simplify matters if we take the position and maintain it by the positive statement that no one of these methods, nor all of them combined, has so far satisfied the ideal in accomplishing the desired result to perfection. Much good can be accomplished if one could succeed in the idea that sterilizing the urinary tract is dependent upon much more than the choice of any drug.(1). Urinary infection is by no means a simple thing. When it is confined to the bladder and renal pelvis, it is

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usually an easy problem to eradicate it; but in almost all cases it is not confined to these structures alone.(3). That a given case of "uninvestigated" pyuria or bacteriuria should either improve or fail to improve, following the administration of a given drug, is not evidence of particular value for or against the efficiency of that drug. Numerous so-called accessory, or predisposing causes of urinary infection must first be eliminated. There are certain well-defined and well-recognized, "intra-urinary", predisposing factors, which may be grouped under the main headings; retention, calculus, new growth, and tuberculosis. The folly of attempting a cure by drug therapy of a urinary infection which is primarily dependent upon one of the above-named mechanical factors, is quite apparent. Concerning the systemic or "extra-urinary" predisposing causes of urinary infection, our knowledge is relatively scant and unsatisfactory. There are those cases of pyuria or bacteriuria occurring during the course of an acute infectious disease, and there is that large group of cases in which it is considered that chronic focal local infection plays a role. Whether our predisposing causes of infection be intra-urinary or systemic, rendering the urine

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antiseptic is obviously ridiculous. Therefore, if accurate information is to be obtained, the essential preliminaries in selecting cases suitable for internal urinary therapy, are, 1) a complete general physical examination, and 2) a complete urological examination. It should be further noted that favorable results can not be expected in far advanced cases, as, for example, bilateral pyelonephritis of long duration, with extensive destruction of renal tissue and lowering of renal function.(4). Some of the articles published on the subject of urinary antiseptics in the past few years have been misleading in that they have failed to emphasize these facts that the urinary infection is practically always developed as a result of changes in the urinary tract from infections elsewhere which first must be treated to obtain a cure.(5).

Among the various opportunities for urological investigation, there is no subject more far-reaching in its importance, and more unlimited in its scope, than that of urinary antiseptics.(6). It presents a large field for medical experimentation. The search for specific drugs goes on without interruption and although the problem has received no small measure of attention from the research investigations in the past few years, the literature reveals a surprising absence of sound experimental and clinical

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evidence to the fitness of any known drug to approach the desired result.(7)(4). Much of the advertising done by the manufacturers of urinary antiseptics makes claims for them which very few urologists are willing to support. An astonishing thing about it has been that such advertising has been printed in the very best American journals. (5).

Probably the most important branch of the subject of urinary antiseptics, and one of the greatest importance as far as the future is concerned, is what may be termed urological bacteriology, including the cultural identification and classification of the bacterial flora found in the urinary tract.(6). A long list of organisms have been reported for urinary infections, but it is full of duplications under different names. Relatively few organisms are common invaders, and the relative frequency of their occurrence in different parts of the tract is fairly uniform. The colon bacillus is found in from 70 to 80% of renal infections. Staphylococcus albus is the next most common invader, being present in about 10% of the cases. Then comes the streptococcus and the proteus vulgaris in about equal frequency, followed by scattered reports of the gonococcus and the typhoid bacillus. The findings for

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the bladder are not so uniform and a much greater variety of organisms have been reported. The tubercle bacillus is probably present in about 5% of all cases.(8). It has been found that staphylococcus growth is aided by alkalinity and delayed by acidity. The reverse is true of Bacillus coli, for its growth in both acid and alkaline urine is luxuriant.(9). It is a primary thought that stagnant, or residual, urines, at body temperature, are excellent culture media for many organisms, particularly the coloh bacillus, whereas free flowing urine does not become easily contaminated, but commonly carries tremendous loads of bacteria beyond the body without infecting it. Well known as is this statement, its truth is not generally appreciated nor given the practical consideration its importance deserves.(1). Experiments show how hard it is to infect the normal urinary tract, and how easy it is to infect the diseased or changed tract.(5). It has also been shown that a very dilute urine materially interferes with the effectiveness of a urinary antiseptic because it dilutes the antiseptic too greatly and because it increases the surface tension of the urine making the penetration of a cell membrane of the organism more difficult. Of course a concen-



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trated urine is in itself some what irritating to the urinary tract.(5)(10). It is a well known fact that antiseptics in urine is quite a different thing from antiseptics in water. There are numerous compounds which are germicidal in high dilutions in water, but which lose this property entirely when diluted in urine, even when in relatively high concentrations. This astounding fact has proved to be a great obstacle.(11).

Urinary antiseptics could well be used in the following infections of the urinary tract which includes pyelitis of infancy, chronic pyelitis of adults, acute pyelonephritis, and in the acute and chronic cases of cystitis. It should also be of value as a prophylactic following urethral instrumentation.(4)(12). Cases of urinary infection, characterized chiefly by frequent and painful urination, and by the presence of pus or bacteria, or both, in the freshly voided urine, are observed very frequently, in either sex, at any age.(13).

The purpose of a urinary antiseptic is to control urinary infections and prevent their exacerbations while, and until, the causes for the production and continuation of the urinary infection are removed.(14). In the selection of an antiseptic, there are many desiderata which should be

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considered. Davis (13) states the ideal urinary antiseptic should be chemically stable, comparatively non-toxic, and non-irritating to the lower urinary tract, which is eliminated, unchanged, by the kidney, and which exerts a definite antiseptic action in high dilution in urine of any reaction. Henline and Leonard add to the definition, "and at a rate by which continuous antiseptic action may be attained.(15).

The object of this paper is to discuss only a few of the many preparations classified as germicides and antiseptics useful in treating diseases of the urinary tract, and to discuss their relative efficiencies from a laboratory standpoint.

## EXPERIMENTAL RESULTS

Experiments were undertaken to determine the anti-septic value of the present day urinary antiseptics in vitro, using normal human urine as a culture medium. The technique as described by Davis in his extensive works with urinary antiseptics was used. (12)(16)(17). A 1% solution of the drug was used in varying dilutions, in urine, and placed in sterile test tubes. A standard loop of a diluted 24 hour broth culture of B. coli and Staphylococcus aureus were inoculated in the urine, and incubated for 24 hours. At the end of this period one standard loop was transferred from each tube to melted agar and plated. The plates were inspected after another 24 hours incubation, and the results recorded. The development of an infinitive number of colonies ( $\infty$ ) proved the corresponding urine tube to have been suitable culture medium for the bacteria; while the sterile plate (O) indicated the efficient concentration of the drug for anti-septic action. The plates were examined under low and high microscopic power by Dr. Edwin Davis, Department of Urology, University of Nebraska College of Medicine.

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Table I

DRUG 1% solution	DILUTIONS													
	200		500		1000		3000		5000		10,000		Control	
	C	S	C	S	C	S	C	S	C	S	C	S	C	S
PYRIDIUM	0	0	0	0	0	0	?	0	∞	0	∞	1,000	∞	∞
UROTROPIN	0	0	0	0	0	0	∞	0	∞	0	∞	1,000	∞	∞
ACRIFLAVINE	0	0	0	0	0	0	0	0	0	0	0	0	∞	∞
CAPROKOL	-	-	-	-	-	-	0	0	∞	100	∞	0	∞	∞

(∞ = infinitive 0 = no growth C = colon bac. S = Staph.)

Experiments were now carried out to observe the secretion of antiseptic urine by man. The antiseptics were administered to normal man, the purpose being not to attempt clinical cures of existing urinary infections, but to demonstrate antiseptic action in specimens of urine voided after drug administration. In each instance a specimen of urine was obtained before the drug was given and this was used as a control, all experiments not so controlled were discarded.

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Specimens of urine were again collected in sterile test tubes at two, four, and eight hour intervals, following drug administration. Two series of tubes were used - one for colon inoculation and one for staphylococcus investigation. Nine ( 9 c.c. ) cubic centimeters of urine were placed in their respective tubes and one standard loop of colon bacillus was inoculated into each tube. The same was done for the staphylococcus. The tubes were then incubated for 24 hours and plated in agar as described already. These organisms were used through out the experiments because they are the most frequent invaders of the urinary tract, and because they are more or less resistant to antiseptics, and they are readily cultivated. Probably the greatest obstacle in the field of investigation is contamination. The individuals who submitted to the experiments were all junior medical students on an average intake of water. Drugs were furnished by the various manufacturers. Preliminary work was carried on first in order to become accustomed to the technique, correct dosage, etc.(22).

Pyridium was the first of the series of drugs to be used. The dosage in this case was 0.4 gm. ( gr. VI ) in the form of a pill furnished by Merck and Co. The men were instructed to report any subjective symptoms they noticed.

URINARY ANTI SEPSIS

Table II

Pt.	Drug	Dose	Sub. Symp.	Results			
				Cont.	2hr.	4hr.	8hr.
	Pyridium	0.4gm.		CS	CS	CS	CS
1.	"	"	Backache	∞ 1000	∞ 1000	∞ ∞	∞ ∞
2.	"	"	Headache	∞ ∞	∞ 1000	∞ 10	∞ ∞
3.	"	"	Nausea, sweat	∞ 1000	∞ 10	10 10	∞ ∞
4.	"	"	Nauseated	∞ 1000	∞ 100	∞ ∞	∞ 100
5.	"	"		∞ ∞	∞ ∞	∞ 0	∞ 10
6.	"	"	Sweating	∞ ∞	∞ ∞	∞ 0	∞ ∞
7.	"	"		∞ ∞	∞ ∞	∞ 0	∞ ∞
8.	"	"	Malaise	∞ ∞	∞ 0	∞ 1000	∞ ∞
9.	"	"		∞ ∞	∞ ∞	∞ ∞	∞ ∞
10.	"	"		∞ ∞	∞ 0	∞ ∞	∞ ∞
11.	"	"	Dizziness	∞ ∞	∞ ∞	∞ ∞	∞ ∞
12.	"	"	Nausea	∞ ∞	∞ ∞	∞ ∞	∞ ∞

Feb. 15, 1932

Urotropin, or hexamethenamine, was next used in our study. The same men were used as before, with the same numbers. Tablets, two each of seven and one half grains were given by mouth. The drug was furnished by Schering and Glatz. Results:

URINARY ANTISEPSIS

Table III

Pt.	Drug	Dose	Subjective Symptoms	Results			
				Cont.	2hr.	4hr.	8hr.
	Urotropin	gr. XV		CS	CS	CS	CS
1.	"	"	Fullness Bladder	1000 1000	0 0	0 0	0 0
2.	"	"		∞ ∞	∞ 0	0 0	0 0
3.	"	"		∞ ∞	∞ 10	0 0	∞ 0
4.	"	"		∞ ∞	∞ ∞	∞ ∞	∞ 0
5.	"	"		∞ ∞	∞ 0	∞ 0	∞ 1000
6.	"	"		∞ ∞	∞ ∞	∞ 1000	∞ 0
7.	"	"	Nausea	∞ ∞	∞ 0	0 0	0 0
8.	"	"		∞ ∞	∞ 0	∞ 0	0 0
9.	"	"		∞ ∞	∞ ∞	∞ 0	∞ 0
10.	"	"		∞ ∞	0 0	0 0	0 0
11.	"	"		∞ ∞	0 0	0 0	0 0
12.	"	"		∞ ∞	0 0	0 0	∞ 0

Feb. 20, 1932

Caprokol, or hexylresorcinol, furnished by Sharp and Dome and Co., were now taken. This was given in gelatin capsules containing 0.15 gm. of the drug in 25% olive oil. Five of them were given, with the warning to limit their intake of water during the day. The results were as follows:

URINARY ANTISEPSIS

Table IV

Pt.	Drug	Dose	Subjective	Results									
				Cont.		2 hr.		4 hr.		8 hr.			
	Caprokol	.75 gm.	Symptoms	CS	CS	CS	CS	CS	CS	CS	CS	CS	CS
1.	"	"	Pain in Abdom.	∞	∞	∞	∞	0	∞	∞	∞	∞	∞
2.	"	"	Cramps in Abdom.	∞	∞	∞	∞	∞	0	∞	∞	∞	∞
3.	"	"		∞	∞	∞	∞	∞	0	∞	∞	∞	∞
4.	"	"		∞	∞	1000	∞	0	∞	∞	∞	∞	∞
5.	"	"	Pain in Abdom.	∞	1000	∞	∞	∞	0	∞	∞	∞	∞
6.	"	"		∞	∞	1000	∞	0	∞	∞	∞	∞	∞
7.	"	"		∞	∞	∞	∞	10	0	∞	∞	∞	∞
8.	"	"		1000	∞	∞	∞	∞	∞	∞	∞	∞	∞
9.	"	"		∞	∞	∞	∞	0	∞	∞	∞	∞	∞
10.	"	"		∞	∞	∞	∞	∞	∞	∞	∞	∞	∞
11.	"	"	Cramps in Abdom.	∞	∞	1000	∞	∞	0	∞	∞	∞	∞
12.	"	"		∞	∞	∞	∞	∞	∞	∞	∞	∞	∞

Feb. 24, 1932

Acriflavine given in 0.2 gm. doses in capsules was the next drug to be used. We had the men on the day before taking the drug, take 4 gms. of sod. bicarbonate every four hours for three doses, in order to be sure that the urine was alkaline on the day of the drug administration. The following results:



URINARY ANTISEPSIS

Table V

Pt.	Drug	Dose	Subjective Symptoms	Results			
				Cont.	2hr.	4hr.	8hr.
	Acriflavine	0.2 gm.		CS	CS	CS	CS
1.	"	"		∞ ∞	∞ ∞	0 0	0 ∞
2.	"	"		∞ ∞	∞ ∞	1000 0	1000 0
3.	"	"		∞ ∞	∞ ∞	0 0	1000 10
4.	"	"		∞ ∞	∞ ∞	0 ∞	∞ 0
5.	"	"		∞ ∞	∞ ∞	0 0	∞ ∞
6.	"	"	Diarrhoea	∞ ∞	∞ 10	0 0	1000 1000
7.	"	"	Diarrhoea	∞ ∞	∞ ∞	∞ 1000	∞ ∞
8.	"	"		∞ ∞	∞ 100	0 0	1000 1000
9.	"	"		∞ ∞	1000 ∞	0 0	1000 0
10.	"	"	Diarrhoea	∞ ∞	∞ ∞	0 0	0 1000
11.	"	"	Dirrhoea	∞ ∞	∞ ∞	0 0	1000 ∞
12.	"	"		∞ ∞	∞ ∞	0 0	0 0

March 2, 1932

The drug used in the above experiment was a french preparation furnished by Poulenc Freres, Paris. This was the drug used by Davis in his earlier experiments.

The next step was to compare the above brand of the

URINARY ANTISEPSIS

acriflavine with the American products. Abbott's neutral acriflavine in the form of a pill - gr. 1/2 - were given to the twelve men for the total dose of gr. VI (0.2 gm.). The following <sup>54</sup>re~~s~~ults were obtained:

Table VI

Pt.	Drug	Dose	Subjective Symptoms	Results									
				Cont.	2hr.	4hr.	8hr.	Cont.	2hr.	4hr.	8hr.		
	Acriflavine	0.2 gm.		CS	CS	CS	CS	CS	CS	CS	CS	CS	CS
1.	"	"		∞ ∞	∞ ∞	∞ ∞	∞ ∞	∞ ∞	∞ ∞	∞ ∞	∞ ∞	∞ ∞	∞ ∞
2.	"	"		∞ ∞	∞ ∞	∞ ∞	∞ ∞	∞ ∞	∞ ∞	∞ ∞	∞ ∞	∞ ∞	∞ ∞
3.	"	"	Headache	∞ ∞	∞ ∞	∞ ∞	∞ ∞	∞ ∞	∞ ∞	∞ ∞	∞ ∞	∞ ∞	∞ ∞
4.	"	"		∞ ∞	∞ ∞	∞ ∞	∞ ∞	∞ ∞	∞ ∞	∞ ∞	∞ ∞	∞ ∞	∞ ∞
5.	"	"		∞ ∞	∞ ∞	∞ ∞	∞ ∞	∞ ∞	∞ ∞	∞ ∞	∞ ∞	∞ ∞	∞ ∞
6.	"	"	Headache	∞ ∞	∞ ∞	∞ ∞	∞ ∞	∞ ∞	∞ ∞	∞ ∞	∞ ∞	∞ ∞	∞ ∞
7.	"	"		∞ ∞	∞ ∞	∞ ∞	∞ ∞	∞ ∞	∞ ∞	∞ ∞	∞ ∞	∞ ∞	∞ ∞
8.	"	"		∞ ∞	∞ ∞	∞ ∞	∞ ∞	∞ ∞	∞ ∞	∞ ∞	∞ ∞	∞ ∞	∞ ∞
9.	"	"		∞ ∞	∞ ∞	∞ ∞	∞ ∞	∞ ∞	∞ ∞	∞ ∞	∞ ∞	∞ ∞	∞ ∞
10.	"	"		∞ ∞	∞ ∞	∞ ∞	∞ ∞	∞ ∞	∞ ∞	∞ ∞	∞ ∞	∞ ∞	∞ ∞
11.	"	"		∞ ∞	∞ ∞	∞ ∞	∞ ∞	∞ ∞	∞ ∞	∞ ∞	∞ ∞	∞ ∞	∞ ∞
12.	"	"	Nausea	∞ ∞	∞ ∞	∞ ∞	∞ ∞	∞ ∞	∞ ∞	∞ ∞	∞ ∞	∞ ∞	∞ ∞

March 9, 1932

URINARY ANTISEPSIS

The startling results we obtained at this point, that is the difference between capsule and pill administration in the same dosage with supposedly the same drug, led us to investigate further in this respect. Abbott's powdered acriflavine were made up into capsules of 0.2 gm. and administered. The results:

Table VII

Pt.	Drug	Dose	Subjective Symptoms	Results									
				Cont.	2hr.	4hr.	8hr.	Cont.	2hr.	4hr.	8hr.		
	Acriflavine	0.2 gm.		CS	CS	CS	CS						
1.	"	"		∞ ∞	∞ ∞	0 0	0 0						
2.	"	"	Diarrhoea	∞ ∞	∞ ∞	0 0	0 0						
3.	"	"	Headache	∞ ∞	∞ ∞	∞ ∞	∞ ∞						
4.	"	"	Nausea - dizziness	∞ ∞	∞ ∞	0 0	0 0						
5.	"	"		∞ ∞	20 0	0 0	0 0						
6.	"	"		∞ ∞	∞ ∞	0 100	∞ 0						
7.	"	"	Diarrhoea	100 60	0 0	0 0	20 0						
8.	"	"	Nausea	∞ ∞	0 100	0 0	0 0						
9.	"	"	Nausea - vomiting	∞ ∞	100 0	0 0	∞ 0						
10.	"	"	Nausea	∞ ∞	∞ 0	0 10	∞ 0						
11.	"	"	Nausea - vomiting	∞ ∞	0 0	0 0	∞ 10						
12.	"	"		∞ ∞	0 0	10 0	∞ 0						

March 16, 1932

URINARY ANTI SEPSIS

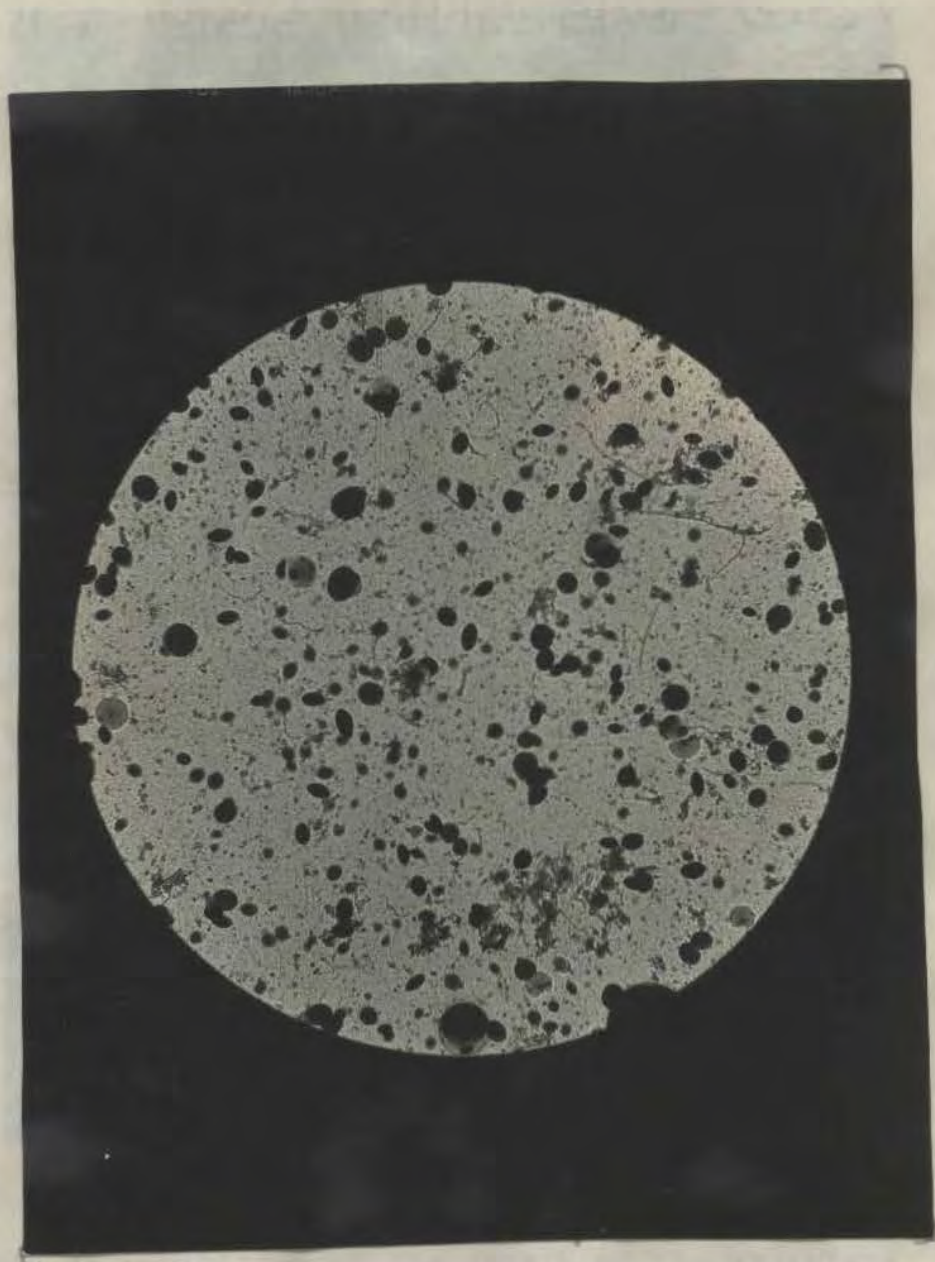
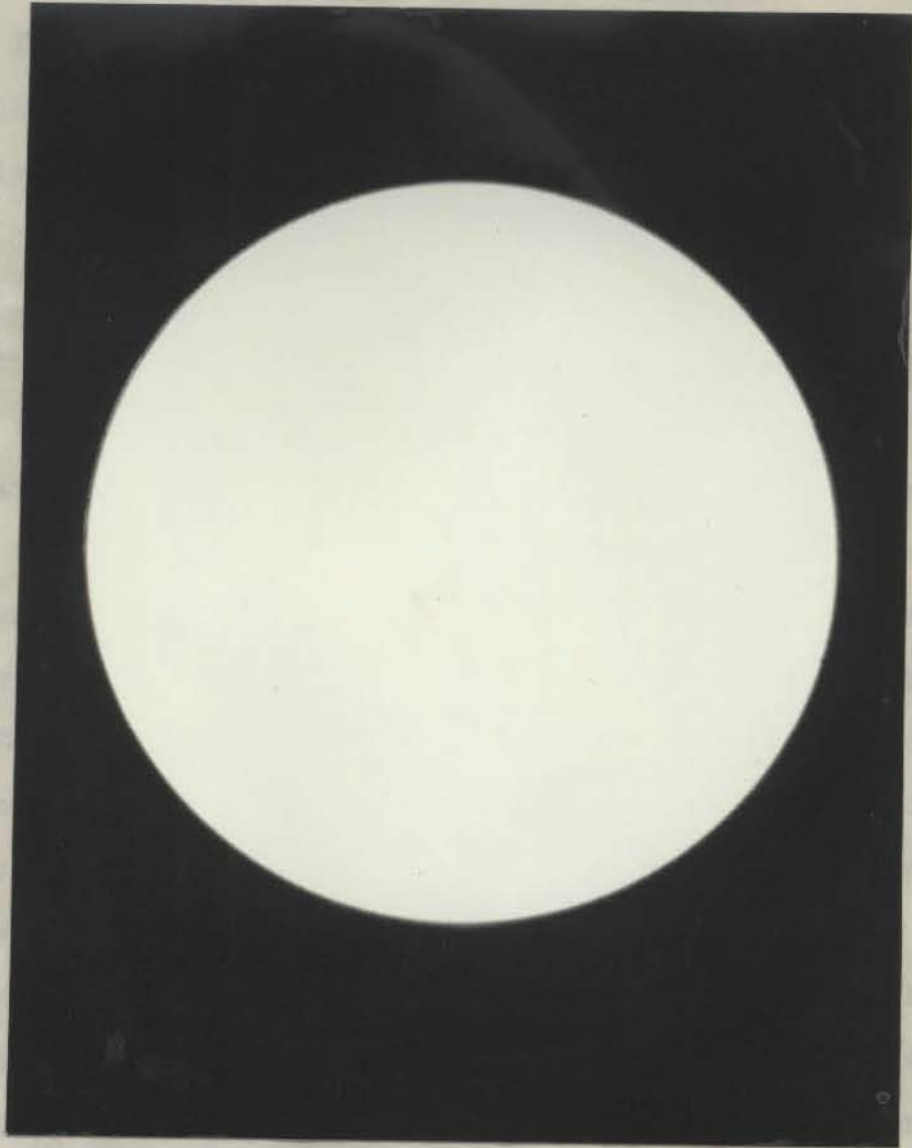


Figure 1

Demonstration by means of micro-photography an INFINITIVE ( $\infty$ )  
plate,

URINARY ANTISEPSIS



The above illustrates a STERILE plate (○), or in other words an inhibition of the growth of the organisms.

## URINARY ANTISEPSIS

Because of the lack of time, this paper being due on April 15, 1932, I had to draw what conclusions I could from the data already obtained in our experimentation with the four drugs.

In the experiment with the different dilutions of the drugs in urine (Table 1, page 9), we find that acriflavine shows the antiseptic action in by far the highest dilutions of any of the other drugs, that is, in the 1:10,000 dilution, acriflavine inhibits the growth of both organisms. Caprokol rates second in this series, being inhibitory to the growth of both organisms in dilutions of 1:3,000, but in a 1:10,000 dilution and upward it shows antiseptic action against the staphylococci only. Both pyridium and urotropin in dilutions of 1:1,000 show inhibitory action against both organisms, but in addition, in dilutions of 1:5,000 staphylococci are inhibited, the colon bacillus growing luxuriantly.

In the experiments carried on with the twelve individuals taking the different drugs orally, we find acriflavine again leading the field by a wide margin, that is, when given in the form of a capsule; in the pill form, the action is nil on both the colon bacillus and staphylococcus. Whether this be due to the salol coating of the pill preventing absorption in the G.I. tract, or due to a delayed time action of the drug

## URINARY ANTISEPSIS

in exerting its antiseptic action in the urine, has not as yet been determined, but a factor we are now working on and one which we hope to solve in the very near future. Acriflavine in either the neutral form of Abbott (Table VII, page 16) or the original French product of Poulenc Freres (Table V, page 14) when given in capsules show a very definite antiseptic action in the four hour specimen of alkaline urine secreted by normal individuals after a single dose of the drug administered orally. The former seems to be a bit more effective in the two hour sample and it also carries over better in the eight hour sample than the French drug. We found two disadvantages in giving the drug, namely, 1) the necessity of giving an alkali in collaboration with the urinary antiseptic, and 2) the symptoms of nausea and catharsis presented by the men. Whether these symptoms were due to the drug itself or to the alkali is not clear, but Davis is prone to believe that it is due to the drug.

Urotropin ranks next in our series (Table III, page 12) exhibiting complete inhibition of both organisms in the four hour sample of urine in 7 of the 12 men. Of the remaining five, four inhibited the staphylococci although the colon bacillus growth was not impaired. The antiseptic action was well carried over the eight hour specimens with five of the men showing a

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complete inhibition of both organisms even as rapidly as in the two hour specimen. The subjective symptoms presented were few, the drug was easily taken and the cost comparatively small.

Caprokol (Table IV, page 13) ran a poor third in the series, but it did exhibit the two facts that Leonard brought out in his experiments with the drug, namely, that the drug has a peculiar experimental affinity for the colon bacillus, even more so than the less resistant staphylococcus, but that the latter is destroyed in far higher dilutions in the urine than is required to kill *E. coli* (Table I, page 9). The four hour sample showed only very weak, irregular antiseptic action of the drug which was completely lost in the eight hour sample. Four of the twelve men complained of cramping pains in the lower abdomen. The drug is very expensive, and is very awkward to give as it must be administered in large gelatine capsules containing olive oil.

Pyridium (Table II, page 11) ranks a very poor fourth in our series. The action on the colon bacillus was nil. The drug did show a weak antiseptic action on the staphylococci in both the two and four hour specimens of urine secreted by the normal men, after a single dose of the drug. This drug is also very expensive, and the subjective symptoms in most of the

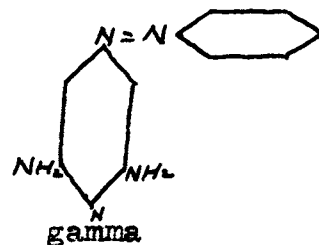
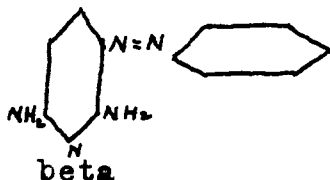


## URINARY ANTISEPSIS

cases was nausea. In the future, we are going to try the pyridium powder given in the same dose as the pill to find if the results of this drug will be similar to the acriflavine experiment.

## DISCUSSION

PYRIDIDIUM:- a monohydrochloride of an azo dye of the pyridine series ( phenyl-azo-alpha-alpha-diamino pyridine hydrochloride ) and a semicolloidal condensation product of the beta and gamma isomers which may be presented structurally as follows:



Pyrididium is remotely related to quinine inasmuch as quinine also may be regarded as a derivative of piperidine and therefore of pyridine. It is to the semicolloidal property of quinine, imparted to it by the oxyquinoline radical, that some authorities attribute its peculiar therapeutic power. Thus, similarly, pyrididium's property in this instance may be assigned to the phenylazo radical. Pyridine itself and its analogues are too toxic for use therapeutically, but with the addition of the radical present in pyrididium, which impart to it its colloidal properties, not only are the bactericidal properties increased, but its toxicity is lowered. (18)(19)(20).

Pyrididium is a fine, microcrystalline powder, of bright

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red color, slowly soluble in cold water, but soluble in boiling water, alcohol, glycerin, petrolatum, and lanolin. It may be administered orally ( tablet ), or applied locally ( solution, powder, ointment ). It is generally used in the tablet form, each tablet containing 0.1 gm., the dosage usually being 2 tablets after each meal. It is rapidly absorbed and eliminated from the system practically unchanged in the urine. The urine is stained an orange-red, the color first appearing within an hour after administration. Pyridium is compatible with practically all remedies except those which contain mercury. (7)(15)(19)(21).

Four outstanding characteristics are claimed by the drug, Pyridium, namely: its marked power of stimulation to the proliferation of epithelial cells, its powerful bactericidal action, its ability to penetrate the tissues, and its rapid elimination through the genito-urinary tract.(20).

Only a very little work, experimentally, has been done in this country with pyridium. It is one of the newest urinary antiseptics, and has just recently been accepted by the Council of Pharmacy and Chemistry. Walther in his work with the drug found that with the average dose per day (0.6 gm.) and presuming that the patient excretes 3000 c.c.

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of urine each day, the pyridium was excreted almost in toto by the urinary tract, but that this would give a concentration of approximately 1:4,500, which he found was too dilute for efficient action. Therefore, he asked the patient to limit his fluid intake to 1500 c.c. per twenty four hours, which would give a concentration of 1:2,000, which he says is within the maximum therapeutic range of the drug. Thomas and Wang agree with Walther that in concentrations of 1:1,000 staphylococcus will be killed in vitro. (20)(23). This does not correspond to our results, however, as we found that the staphylococcus was killed in dilutions as high as 1:5,000. (see Table I). Further, we do not agree with them in that they they found that the colon bacillus was killed in as low a dilution as 1:400, whereas in our series there was no colon growth in dilutions around 1:3,000, which tends to support the manufactureres claims that the drug is antiseptic in high dilutions.

Clinically, the drug has fared better. The seminal and prostatic fluids are definitely stained by pyridium soon after medication is instituted, and spermatozoa often show the presence of the dye, which also tends to prove a

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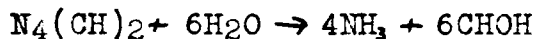
penetrating power of immense value in combating infections of these structures.(18). Purge, (19), has concluded that the drug possesses the greatest power of penetration than any other substance heretofore used. According to Wolbast,(21), pyridium as a general urinary antiseptic proved to be decidedly effective as an adjuvant to instrumental measures in pyelitis, and other upper urinary tract infections of staphylococcus and Bacillus coli origin. He considers it a promising addition to our therapy, but that a further study is required. Deakin,(24), found that the average duration of a control group of cases of acute gonorrhoea was 109 days, while the average duration of the group on pyridium was 71 days. Also, there was a marked decrease in the frequency with which posterior urethritis and prostatitis developed in the pyridium group. Whereas Pugh, (15), claims the drug is bactericidal for all organisms infecting the urinary tract; Thomas and Wang claim that in no instance is the effect of B. coli inhibited.

In closing the discussion on pyridium we might add that to us the drug has the requirement of being eliminated rapidly, is non-irritating to the lower urinary tract, and is chemically stable; but experimentally, it does not prove to be anti-

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septic - the action on staphylococci very slight, and on the colon bacillus, nil. This with the symptoms the men presented upon taking the drug, and the high cost of the drug lead us to look further in search of an ideal urinary antiseptic.

UROTROPIN: (hexamethylenetetramine) a white crystalline substance, readily soluble in water, tasteless, colorless, and is made by the interaction of ammonia and formic aldehyde. In acid solutions, it at once begins to decompose again:



Its action as a urinary antiseptic depends on this liberation of free formaldehyde. Hexamine is non-toxic, it is rapidly absorbed, circulates in the blood unchanged, and begins to be excreted in the urine in about 20 minutes, reaching its maximum amount there in about 4 hours.(25). Urotropin is perhaps the cheapest, the most conveniently given, and the most easily taken of all the so-called urinary antiseptics.(5). It should never be given except in conjunction with a definite acidifying agent, and in the minimum of 8 ounces of water to every 10 grains of the drug. It is usually supplied in 5 and 7 1/2 grains tablets, the dosage - 5 to 15 grains two to four times daily.(18).

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This drug was first prepared in 1860 by Butlerow. The demonstration of formaldehyde as a decomposition product in acid urine by Nicolaier, in 1895, offered to the medical profession a new opportunity in the treatment of urinary infections; antiseptis by internal medication. Richardson (26) described it as possessing high urinary antiseptic value in the treatment of typhoid fever. Churchman (27), in 1906, observed that the effect of hexamine as a urinary antiseptic is expressed in an inhibition of bacterial development rather than as a germicide per se. (23).

No detailed experimental investigation of the drug's activity as a urinary antiseptic seems to have been made until 1912, when Burnam (28) showed that in customary doses (5 to 10 grains t.i.d.) of methenamine, not more than one patient out of five would show any formaldehyde in the urine. The following year Hinman (29) undertook a thorough study of the factors influencing the excretion of methenamine and its conversion into formaldehyde in acid urine. Of the 318 specimens of bladder urine examined, 64% were found to contain so little formaldehyde (less than 1:30,000) as to be devoid of antiseptic value. Of the remainder, only 17% showed formaldehyde in concentrations sufficient for complete

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bacteriostasis and only 5% were germicidal. Hinman concluded that methenamine is of no value at the kidney level, because the urine does not remain in the renal pelvis a sufficient length of time to permit the conversion of the drug into formaldehyde, and that the same condition is obtained in the bladder if urination is frequent. This work has since been confirmed both in this country and abroad by Walker, Culver, and Sutton.(30). The earlier claim that Urotropin is itself a diuretic was entirely disproved by the work of Ruh and Hanzlick in 1922.(31). Moderate doses of the drug will cause hematuria in a small number of individuals, the bleeding being due to the production of a hemorrhagic cystitis. Bloedorn and Houghton (32), were not able to produce it at will, and they believe that it occurs only in those individuals who have an idiosyncrasy to the drug. The intravenous use of urotropine does not seem to be necessary or even justified in view of the rapid absorption obtained upon oral administration; however, it has been successfully used at the Mayo Clinic in 76 cases of acute and sub-acute infection.(33).

Bacteriological experiments with the drug urotropine have been very interesting. In a series of experiments on rabbits with induced infection of the urinary tract, Hemholz



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and Field (34), have come to the conclusion that hexamethen-amin is superior to mercurochrome and hexylresorcinol as a urinary antiseptic in cases of infection produced by staphylococcus and colon bacillus. Levy and Strauss (35), in their studies of the drug come to the conclusion the hexamethylenamine per se even up to a 10% solution has neither bactericidal nor marked inhibitory properties. Since the drug is never present in the urine in concentrations as great as 10%, it must be concluded that when an inhibitory or bactericidal action is shown in the urine it can not be due to the drug itself, but formaldehyde. Stockman (25), of Scotland says that hexamine in a strength of 1:5,000 is not strong enough to be bactericidal, but in our series of dilutions (Table I, page 9) in the same dilution, the staphylococcus was inhibited entirely, the colon bacillus, infinitive. Thomas and Wang (23) say that no reliance can be placed on hexamethylenamin as a urinary antiseptic, since formaldehyde itself is a weak disinfectant, which is only liberated in the presence of acid urine. Furthermore, acid urine is no criterion to insure a high formaldehyde content, as, frequently they were disappointed to find a very low concentration of formaldehyde in a very highly acid specimen of urine.

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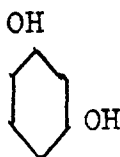
Clinically, the drug had wide spread popularity up to the time of Hinman's work, and though still extensively used, the newer drugs are gradually taking its place. As stated before we are pleased with the experimental results we obtained with the drug, seven of the twelve men showing bactericidal urine for both staphylococcus and colon bacillus in the four hour sample, the relatively few symptoms, the cheapness of the drug; but we know the wide span between experimental results and clinical results which we will discuss in the next part of this thesis, so will reserve our conclusions until the end.

CAPROKOL: (hexylresorcinol) is a white wax-like solid, insoluble in water, but soluble in olive oil.(25). It is claimed to be administerable by mouth, chemically stable, non-toxic in therapeutic doses, non-irritating to the urinary tract, bactericidal in high dilutions in urine of any reaction, and is secreted by the kidney unchanged in sufficient percentage to impart active bactericidal properties to the urine.(36)(37). The dosage internally, from 0.15 to 0.6 gm. three times a day, supplied in the form of an olive oil solution in a gelatin capsules. Children tolerate relatively larger doses of the drug than adults.(38).

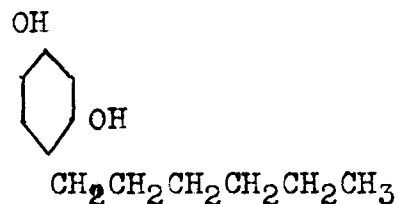
Hexylresorcinol is an alkanized resorcinol. The

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resorcinols were first synthesized in 1913 by Johnson and examined by Rettger, who found that, as the series of alkyl resorcinols were ascended, the bactericidal properties of the product increased very rapidly. It was recently introduced as a urinary antiseptic following the investigation of Leonard, at Johns Hopkins hospital, during the years of 1914 to 1924. He found that coincident with this sharp rise of bactericidal power, there was a sharp decrease of toxicity. (39). The hexyl derivative of resorcinol exhibited a phenol coefficient of 46 - the sixth C atom straight derivative as follows:



Resorcin



Hexylresorcinol

Hexylresorcinol is 46 times more potent than phenol as a germicide and 150 times more powerful than resorcinol. It is believed to be one of the most powerful organic germicides ever described. Unfortunately, it is detoxicated in the body by being conjugated previous to its excretion in the urine and conjugated compound is inert. A small portion ( free hexylresorcinol ) of it seems usually to escape detoxication, but

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the amount is never more than a very small percentage of the quantity ingested.(25). Depending, as it seems we must, upon the elimination of unconjugated hexylresorcinol in order to obtain bactericidal urine, it is not surprising that some individuals would be found to conjugate this substance more completely than others, or even the same individual might vary in this regard from week to week.(40).

Experimentally, according to Leonard, urine examined after a single dose of hexylresorcinol reveals bactericidal properties in 53% of the cases the 1st hour, 92% in the 3rd hour, and 56% in the next 18 to 24 hours after administration.(41). In comparing our results after a single administration of the drug we find no such figures. Not one man excreted bactericidal urine at any time for both the organisms. Leonard makes a sweeping statement when he says he has never encountered a normal man who would not secrete bactericidal urine with fair regularity after a day or two on doses 0.6 gm. t.i.d.(40). Tests of the bactericidal action of the drug in normal urine were made by innoculating the urine with strains of B. coli and staphylococcus, and it was found that the organisms were destroyed in dilutions of 1:10,000 and upward in both acid and alkaline urine (39).

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This was not born out in our experiments ( Table I, page 9 ) as we had an abundant growth of colon bacillus at the same dilution, although the staphylococcus was inhibited.

Two important facts were brought out by experiments with hexylresorcinol in normal man should be emphasized, for the reason that they probably bear some relation to the clinical results to be reported. Leonard found that the drug would destroy staphylococcus albus in far higher dilutions in urine of any reaction than are required to kill B. coli; yet of the 251 specimens of urine that were recorded, 150 of them were bactericidal, 137 killed the colon bacillus, while 53 destroyed the staphylococcus under identical conditions. On this basis, it was predicted that hexylresorcinol would prove to be more generally efficient in B. coli infections of the urinary tract than those due to the staphylococcus. The reverse is true.(40).

Clinically the use of alkalis and diuretics are contraindicated. Leonard brings out the fact that it is absolutely essential that the ingestion of large quantities of fluids and of diuretic drugs be avoided during treatment with hexylresorcinol. In this instance one is dealing with a compound which is most active, in the concentrations

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appearing in the urine, at the lower range of surface tension. Not only does dilution of the urine through the ingestion of large quantities of water, or diuretic drugs, result in the lowering of the concentration of the hexylresorcinol in the urine, but concentrations of the germicide which would otherwise be highly bactericidal are inactivated by the rise of the surface tension of the urine which accompanies dilution.(30). Henline (41) in a series of 50 cases of chronic urinary infections of durations varying from 6 months to 14 years, and which has resisted other treatment for periods varying from one to forty months, obtained complete disinfection of the urinary tract with hexylresorcinol in all but three cases (92%). He avoided diuresis. On the other hand, Helmholtz (42) in a series of 14 cases of chronic urinary infection of duration varying from 6 weeks to 14 years, observed complete disinfection of the urinary tract with hexylresorcinol in only one case. He employed active diuresis. As to the alkali question, Leonard and Frobisher (10) and Leonard and Wood (43) have come to the conclusion in their work that hexylresorcinol in acid or alkaline urine is equally active; yet the diuretic properties of the therapeutic dose of sodium bicarbonate may be sufficient to inactivate the drug in the urine.

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The question frequently comes up as to whether or not hexylresorcinol therapy should be considered as contraindicated in nephritis. Leonard and Scott (38) say that the drug has been administered in full doses to a number of adults suffering from chronic nephritis, complicated by urinary infection, and in none of these cases has there been the slightest evidence of harm, while in some there has been a very definite benefit.

Brown (39) endorses Leonard's claims for the drug which he considers undoubtedly a most valuable adjunct to our present means in the treatment of infections of the urinary tract, but adds that approximately 50% of the 63 patients of his series showed gastro-intestinal disturbances of varying extent. Also, that the expense of the drug is one of the greatest objections. Thomas and Wang (23) admit the drug is the most scientific urinary antiseptic as yet described, but that its antiseptics in the urine is not constant. The drug seemed to be disagreeable to most of their patients on account of the size and number of the capsules to be swallowed, which must be considered with a patient with an unsettled stomach. Stockman (25) concludes that the drug reduces the number of organisms and relieves the symptoms promptly enough

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but it is not especially effective in eradicating the infection. So we find that in the end we have a drug highly praised by Leonard and a few others - both in the experimental and clinical test, but with our results, awkwardness in giving the drug, the expense of it, and the symptoms presented by the individuals taking a single dose of it all taken together, we cannot support its use.

Acriflavine: (diamino-methyl-acridium chloride) is a brownish-red, odorless, granular powder. It is soluble in about 3 parts of water; incompletely soluble in alcohol; nearly soluble in ether, chloroform and the fixed oils; the aqueous solution is brownish-red in color, and fluoresces on dilution.(44). Laboratories in Europe and the large clinics of that continent have extensively investigated the aniline dyes. Based on the fact that they stain and are highly toxic to pathogenic organisms but less injurious to the human cell, acriflavine is a product of aniline dyes and has the following properties: it is not impaired by the addition of serum, it does not coagulate protein substances, and in high dilution inhibits the growth of staphylococcus and the colon bacillus.(45). This drug, therefore, should theoretically



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be of clinical value in the treatment of various infections of the urinary tract. As early as 1917, Davis's (4) attention was attracted to acriflavine by publications in the English literature by Browning and others ( the Bland Sutton Institute of Pathology, Middlesex Hospital, London ) who showed the antiseptic action of this drug to be increased in the presence of serum. Davis obtained a small sample of the drug from Browning and was the first in this country to report on acriflavine as an internal antiseptic. His results seemed encouraging.(46). In May, 1923, at the meeting of the American Urological Association, Davis again reported the drug's internal use. His conclusions were then that its use was still in the experimental stage. Although there has been no quantitative estimation of the amount of the drug appearing in the urine, it is not in evidence in any other excretion and is probably completely eliminated by the kidney.(12). When used as an internal urinary antiseptic, the drug may be given in capsules or tablet form - the dosage usually being 0.1 gm. t.i.d. An alkali must be given with the drug to insure the urine to be alkaline. Sodium bicarbonate, 4.0 gms. t.i.d.

Experimental work with this drug has largely been due to Davis. In his preliminary work, he reported that the drug

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inhibited the colon bacillus and staphylococcus in as high a dilution as 1:100,000. The drug was then given normal men in capsules containing 0.2 gm. doses, together with 4 gms. of sodium bicarbonate every four hours. The technique used corresponds to our experiments. His conclusions at that time were that "acriflavine administered by mouth to normal individuals is secreted in the urine in sufficient concentrations to render the urine an unfit culture medium for the colon bacillus and staphylococcus, providing the reaction of the urine is alkaline." (12). Stokes (45) in 1923, supported Davis in his experimental findings on the drug, and added that in acid urine, the staphylococcus is not nearly so easily killed; whereas, the colon bacillus in acid urine requires an exposure to a solution not less than 1:5,000. Davis again ran series of experiments in 1924 and his conclusions were again in support of his earlier views; more definite clinical tests had been worked out.

In the clinical trial of acriflavine, Davis (4) roughly classified the following: 1) Acute Urinary Infections, including acute cystitis and non-surgical kidney infections, with staphylococcus and the colon bacillus in the urine. Out of 18 cases, in 13 there occurred an improvement characterized by a drop in the temperature, a cessation of the bladder

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symptoms, and a disappearance of the pus and bacteria from the urine coincident with the starting of the dye. In the remaining 5 cases, there was apparently no effect. Two patients had recurrences of symptoms three months later, but it is safe to say that 50% of the others have remained well over a period of several months. 2) Chronic Urinary Infections, including chronic cystitis and chronic pyelonephritis. The results were not as good as those obtained in the acute series. Out of a total of 27 cases, there were 11 in which the treatment produced no appreciable effect. The remaining 16 showed distinct improvement of the bladder symptoms with a macroscopic and microscopic clearing of the urine, together with a lessening of the number or a complete disappearance of bacteria from the urine. The discouraging feature of the chronic series was the marked tendency toward recurrence of infection in the urine after discontinuing the dye - 12 of the 16 recurring after the urine became drug free. 3) Acute Anterior Gonorrhoeal Urethritis. Acriflavine administered orally is not a dependable prophylactic for preventing the extension of the infection to the posterior urethra. 4) Acute Posterior Gonorrhoeal Urethritis. Acriflavine administered orally is of benefit in this condition in lessening the duration and the severity of the acute symptoms.

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The clinical experiences of Stockman (25), however, have not been as encouraging. He states that though the drug has marked bactericidal properties in vitro, the urine did not prove to have any marked bactericidal properties in cases of *Bacillus coli* and mild septic infections, and there took place merely a certain amount of inhibition of the bacterial growth. Gray (18), in a recent article, concludes that acriflavine is not as dependable or as useful as some of the newer dye preparations. The oral administration of acriflavine is not without its contra-indications. Approximately 30% of Davis's patients reported slight nausea or a mild catharsis, although this in part may be explained on the doses of sodium bicarbonate. (4). It is suggested that the use of acriflavine by intravenous injection is dangerous.(47).

## THE CLINICAL APPLICATION OF EXPERIMENTAL DATA

The next consideration of the subject of urinary antiseptics is the most difficult question; the clinical application of experimental results. To attempt to prove conclusively the clinical value of a given "experimental" urinary antiseptic is to enter into a problem of far greater complexity than the original laboratory investigation. The treatment of each case is an individual clinical experiment, which is necessarily lacking the "control" which we are able to apply to laboratory experiments. (6). Stockman (25) says that only very little help in overcoming the inherent difficulties presented in the treatment of infections of the genito-urinary tract by means of medicines administered by mouth can be got from the kind of information yielded by experiments carried out by test tubes and bacterial cultures. The conditions are too widely different.

Among the many confusing variable factors which enter into each clinical trial, probably the chief cause for inaccuracy in interpretation of results is the spontaneous or unexplained day to day variation which is frequently observed in the pus and the bacterial content of the urine of a given individual.

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That urine which is cloudy and infected today may be clear and sparkling tomorrow, for no known reason.(6). Further, fresh supplies of active living organisms are constantly contributed from the deeper tissues of the infected urinary passages, from the prostate or seminal vesicles, and thus the infection may be kept up and renewed indefinitely. Also, once the urine is infected, it forms a favorable culture medium which is continually being reinforced by blood, pus, and general organic debris that is present, and these elements may in addition absorb and bind a considerable part of the remedy and thus diminish its effective action on bacteria.(25).

Coincident with these variations in the urine, we are accustomed to seeing alternating periods of exacerbation and spontaneous improvement in the clinical symptoms. Inaccuracies in the interpretation of clinical results also creep in through the improper selection of cases - of which we mentioned earlier in the report.

In view of the numerous obstacles in the way of obtaining accurate and reliable clinical data, it may, therefore, be stated that the clinical efficiency of a given "experimental" urinary antiseptic must be determined by the average opinion of

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a number of competent, unprejudiced observers, each of whom has accurately tabulated results in a series of cases sufficiently large to arrive at some conclusion. As yet, no internal urinary antiseptic has stood the test. We must, therefore, further modify our definition of the ideal urinary antiseptic. We must distinguish between the "experimental" and the "clinical" internal urinary antiseptic, and add that it must be of distinct, proven clinical value.(6).

Careful observation will often indicate the most effective antiseptic for the particular case, and a daily check of the urine will show whether it is producing the expected results or whether a change to another drug is indicated.(5). Urinary infections may be treated by diuresis, or they may be treated by urinary antiseptics. All experimental evidence available indicates decisively that these two methods of treatment should never be combined.(30). Whereas we have new drugs both for oral and intravenous administration, and these drugs represent undoubted progress and are exceedingly valuable therapeutic agents which will make sterilization of the urinary tract less difficult than it has been in the past, even now such sterilization is not an easy or simple process.(1).

## CASE REPORTS

The following cases merely represent the typical manifestations of urinary infection. They in no way help to prove one drug is better than another, because the cases were not properly controlled during their stay at the hospital, or properly followed after their release. As already pointed out in an early part of this paper, to go into such a clinical experiment requires much time and leads one into a field of very complex difficulties. I have only made them a part of this work to point out the importance of removing any foci of infection in the treatment of such cases, and not to expect a drug to cure a pyuria simply because it is listed as an urinary antiseptic.

CASE I: A young woman, age 24, white, married, entered the University hospital Oct. 14, 1931, having active labor pains since the night before. Version was done with the delivery of a dead fetus. A second degree tear of the perineum was repaired at the time of delivery. The patient ran a normal convalescent period for 13 days, but at that time developed a temperature of 101, headache, backache, more so on the right side. The



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physical examination at that time was negative, but the urine (catheterized specimen) showed a 1 plus albumin, 50 pus cells per high power field, with a few epithelial cells and casts. The blood count showed a leucocytosis of 16,650. The symptoms increased in severity for the next three days - the fever going as high as 104 - and the diagnosis of "pyelitis", right side, was made. The patient was put on Urotropin gr. X and Sod. acid phosphate gr. XXX Q.I.D. for one week. At this time her temperature was down, the symptoms relieved, and the urine negative with the exception of a few pus cells in a high power field. The patient was dismissed in a few days.(36591).

This case of pyelitis following pregnancy demonstrates in all probability secondary infection from the genital tract coupled with a lowered resistance of the patient. Urotropin in this case probably did much to relieve the woman from her symptoms - although we do not know whether another drug would not have done just as well in causing the improvement.

CASE II: Man, age 25, white, single, entered the University hospital, Feb. 22, 1931, complaining of a constant, sharp pain in the left lower abdomen and back that had started one week

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ago, and had required several "hypos" of morphine for relief. The physical examination showed very badly infected tonsils and teeth, tender rigid lower abdomen, and hyperesthesia over left flank; otherwise, negative. The patient said he felt something "pass" in his urine the second day he was in the hospital, and the pain eased up. X-rays of the G.U. tract were negative; cystoscopic examination showed the presence of an acute cystitis. The diagnosis was made of "acute cystitis", probably as result of the badly infected tonsils and teeth. The patient was placed on Acriflavine gr. 1/2 and Sod. bicarb. t.i.d. and sent home.(34402). Tonsillectomy was refused.

As long as the patient has his infected tonsils acting as a foci of infection, we can hope for no good from the medication he is receiving. Of course, we can not forget that the cystitis may have been a result of a stone, and if that is the case the drug should promptly clear up the infection.

CASE III: Man, age 32, white, married, entered the University hospital, Feb. 1, 1931, complaining of frequency and burning on urination, and severe pain in groins; one other attack one month ago. The physical examination was essentially negative with the exception of suspicious tonsills and tenderness over

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the region of the bladder. The examination of the urine showed the presence of a 1 plus albumin, 50-60 pus cells per high power field, and many epithelial cells. Cystoscopic examination revealed a definite cystitis had formed; ureteral catheterization and pyelograms showed no renal calculi, but the urine showed signs of pyelitis on the left side. The diagnosis was made of left "pyelitis" and "acute cystitis", and the patient placed on acriflavine gr. 1/2 and citrocarbonate drams 1 t.i.d. Tonsillectomy was refused and the patient was dismissed, after being in the hospital three days. The patient returned in 3 weeks and his tonsils were removed. He was dismissed again with the same therapeutics to follow.(34164).

This again demonstrates the importance of foci of infection in dealing with this type of patients; otherwise medication is to no avail.

CASE IV: Man, age 42, white, married entered the University hospital Sept. 29, 1931, complaining of pain in the lower abdominal region, frequent, burning urination, and dull frontal headache. The patient gave a history of having typhoid fever and septic sore throat last May, from which time he dates the beginning of the present symptoms. The positive points in the

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physical examination were a very advanced pyorrhoea of both upper and lower jaws, some tenderness but no rigidity in the abdomen, and some tenderness in the left flank. The urine at this time was essentially negative except for a few pus cells per high power field; the blood showing a slight leucocytosis of 12,200. X-rays of the teeth confirmed the diagnosis of a destructive pyorrhoea. The diagnosis of pyelitis secondary to oral sepsis was made, and a complete alveolectomy performed two weeks after entrance. The patient was placed on acriflavine gr. 1 1/2 and soda bicarbonate gr. X t.i.d. Patient was dismissed eight days after operation feeling in fairly good condition, the pyelitis having been cleared up. (36184).

The question naturally arises in this case as to whether or not the typhoid fever had more to do with this case than the condition of the mouth. The literature presents many men giving urotropin routinely after typhoid cases for disinfection of the gall bladder, genito-urinary tract, and digestive tract. However, teeth offered a very good source of infection for a pyelitis and were considered the etiological factor in this case.

CASE V: Woman, age 58, white, married, entered the University

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hospital, Nov. 1, 1931, complaining of continuous pain in the lower abdomen, nervousness, frequent, burning urination, and occipital headache. Patient stated she had had these attacks for the last number of years, are progressive in nature, the last attack coming on 6 weeks ago. The physical examination was negative - tonsils and teeth having all been removed. The blood was negative; the urine showing a trace of albumin, a few white blood cells and epithelial cells. X-rays of the G.I. tract were all negative. The condition was thought to be largely mental in nature, although there was evidence of an acute cystitis. This was treated with Urotropine gr. X and Sod. acid phosphate gr. XV t.i.d., along with sedatives for her nervousness. The urine cleared up 16 days after admission, the patient improved, the therapy discontinued and the patient dismissed. (36806).

An etiological factor was not established in this case, and return of the symptoms is quite probable. It would be interesting to know the follow-up history on this case.

CASE VI: Schoolgirl, age 8, white, entered the University hospital, Oct. 20, 1931, complaining of headache, weakness, spells of high fever, and "anemia". Patient gives a history of being

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in the hospital a number of times before - tonsillectomy in 1928, acute sinus infection in 1929, pyelitis in 1930. The child at this time showed many white blood cells per high power field with many epithelial cells. The temperature ranged from 99 on entrance to 104 on the second day - and very irregular thereafter. The blood was not unusual except for a slight leucocytosis of 13,300. X-rays of the sinuses showed evidence of old infections in both antrums; of the kidney, possibly slight widening of the major calices, but no gross deformity. The diagnosis of chronic pyelitis resulting from sinusitis was made and the patient placed on pyridium gm. 1 t.i.d. Symptomatic treatment for the sinuses was advised by the consultants. The patient showed only an occasional pus cell in the urine 33 days after entrance, or three weeks after the beginning of the urinary antiseptic. Patient was dismissed, but referred back to her original doctor for further observation. (36004).

Pyelitis in childhood is an important disease. An ideal urinary antiseptic could find fertile fields for cases such as these. The sinuses here will no doubt cause recurrence of the pyelitis in time to come.

## CONCLUSIONS

Our conclusions in this work are purely experimental and in no way evaluate the clinical results that can be obtained with their use in the various infections of the urinary tract.

1) ACRIFLAVINE: exhibits very definite antiseptic action in alkaline urine four hours after the oral administration of the drug to normal individuals. The drug should be administered in the form of a capsule, doses 0.2 gm.. Acriflavine inhibits the growth of colon bacillus and staphylococcus in alkaline urine in dilutions of 1:10,000 and higher.

2) UROTROPIN: exhibits definite antiseptic action in acid urine for both B. coli and staphylococci growth four hours after the oral administration of the drug. It inhibits the growth of both organisms in urine in dilutions of 1:1,000.

3) CAPROKOL: shows only weak, irregular antiseptic action for both organisms after oral administration of the drug. The growth of both organisms is inhibited in dilutions in the urine of 1:3,000.

4) PYRIDIDIUM: the antiseptic action of this drug after oral

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administration is practically nil in regard to the colon bacillus; only weak, irregular inhibitory action is demonstrated on the staphylococcus. In dilutions of 1:1,000 in urine the drug inhibits the growth of both organisms.

5) We have to make up our minds that we do not as yet possess a perfect urinary antiseptic. The publicity given the antiseptics in the past few years makes it advisable to redirect the attention of the profession to the need of removing the causes of urinary infection, as well as treating the patient with the urinary antiseptics. Perhaps further investigation will reveal an urinary antiseptic which will either cure the disease or shorten its course.

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