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## A NEW GERMICIDE FOR USE IN THE GENITO-URINARY TRACT: "MERCUROCHROME-220"

PRELIMINARY REPORT OF EXPERIMENTAL AND  
CLINICAL STUDIES\*

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During the past two years the research work in the laboratories of the James Buchanan Brady Urological Institute has been given over largely to the study of antiseptics with a view particularly to the development of drugs applicable to the genito-urinary tract. Attention was first directed to internal antiseptics, since Hinman<sup>1</sup> had previously shown in our laboratories the questionable value of hexamethylenamin. Starting with the remarkable selective activity of the kidneys on phenolsulphonaphthalein, as shown by the work of Abel and Rowntree<sup>2</sup> and developed as a functional test in our clinic, we tried to attach other chemical agents to phenolsulphonaphthalein and thus produce an effective internal urinary antiseptic. Some interesting drugs were produced and studied by Davis and one of us (E. C. W.<sup>3</sup>). The war interrupted these studies, but the urgent need of really effective antiseptics for local use in the genito-urinary tract induced us later to concentrate on this problem. Browning was visited in London by one of us, and sufficient quantities of his flavines were obtained and sent to Baltimore. As a result of experiments and clinical use in this clinic, Davis and Harrell<sup>4</sup> recommended the use of acriflavine in the treatment of acute gonorrhoea, and this form of therapy was then used with good results in certain venereal clinics of the American Expeditionary Forces.

Impressed with the possibilities of using dyes as a basis for the development of therapeutic compounds, we have concentrated our efforts on the production of new drugs possessing the penetrating qualities of dyes while at the same time being germicidal and relatively nontoxic and nonirritating. The number of compounds that have been and are being produced in the pursuit of this research is considerable. From among them

the substance reported on in this paper has been selected for extended study. In mercurochrome-220 we have a drug of demonstrated germicidal value. The speed with which some old infections of the bladder and kidney pelvis have disappeared after its use is striking, and the absence of irritating and toxic qualities, together with the ability of the patient to retain a 1 per cent. solution for hours without discomfort, are sufficiently proved to establish the possibilities of the drug in these conditions. For the first time, we have a drug of great germicidal strength that can be tolerated in the human bladder for several hours, which establishes an ideal condition from the standpoint of its sterilizing effects.

Its value in colon and staphylococcus infections has led us to apply mercurochrome-220 to gonorrhoea and chancroidal ulcerations, our investigations having been carried on under the grant recently made us by the Interdepartmental Social Hygiene Board for research in the prevention and treatment of venereal diseases. Our series of cases so far is limited, but the demonstration of the sterilizing value of the drug in the urethra, bladder and kidney pelvis is promising enough to warrant this early publication.

### CONSIDERATIONS GOVERNING SYNTHESIS OF A NEW URINARY GERMICIDE

In synthesizing a drug for local use as a urinary antiseptic, it was sought to combine the following properties: (1) ready penetration of the tissues in which the infection exists; (2) lack of irritation of the drug to tissues; (3) high germicidal activity; (4) ready solubility in water and stability of the solution; (5) freedom from precipitation in urine, and (6) sufficiently low toxicity to avoid systemic effects from the small amount of the drug that may be absorbed.

In order to meet the first requirement it was decided to make use of a penetrating dye, not necessarily a germicide of itself, but serving merely as a carrier in which a germicidal chemical group could be substituted. The clinical experience that the basic dyes such as fuchsin, brilliant green, crystal violet, and, in some cases, the flavines, are too irritating to the mucosa of the urinary tract for general use suggested the use of acid dyes. This class of colors, which includes as its commoner representatives the phthaleins and most of the azo dyes, offers a wide range of choice. From purely chemical considerations it might be predicted that the basic dyes would be more irritating than the acid dyes. The former are salts of weak bases, and therefore their solution must have an acid reaction. The acid dyes, on the other hand, are used as sodium salts, and solutions of them necessarily have a neutral or slightly alkaline reaction, depending on whether the free dye is a strong acid, such as a sulphonic acid, or

\* From the James Buchanan Brady Urological Institute, Johns Hopkins Hospital, with the aid of funds granted by the Interdepartmental Social Hygiene Board for research in the prevention and cure of venereal diseases.

1. Hinman, Frank: *Urinary Antisepsis*, J. A. M. A. **65**: 1769 (Nov. 20) 1915.

2. Abel and Rowntree: *J. Pharmacol. & Exper. Therap.* **1**: 231, 1909.

3. Davis and White: *J. Urol.* **2**: 107, 1918. Davis, White and Rosen: *J. Urol.* **2**: 277, 1918.

4. Davis and Harrell: *J. Urol.* **2**: 257 1918.

a weak acid, such as a phthalein. Since the tissues are generally more sensitive to acidity than to alkalinity, this reasoning led to the choice of an acid dye as the basis of the synthetic germicide.

The extensive use of eosin as a cytoplasmic stain at once suggested its use as a suitable dye of this class. However, it does not lend itself to chemical modification, because those positions in its molecule susceptible to substitution by other chemical groups are already occupied by bromin. On the other hand, it was found that the closely related substance dibromfluorescein could undergo substitution by the germicidal group we chose and still retain practically the same tinctorial properties that eosin itself possesses.

Mercury was chosen as the active germicidal principle to be substituted in the dye molecule. Virtually the only form in which this metal has heretofore been used in the urinary tract has been that of the chlorid or cyanid salts. The chlorid is so extremely irritating that only very dilute solutions (1:30,000) are tolerated, and it is extremely doubtful whether such solutions, especially in the presence of urine, exert much effect on the infection. Concerning the use of the cyanid there is little available information. In the case of either salt, however, the degree of penetrability is uncertain and in all probability is slight.

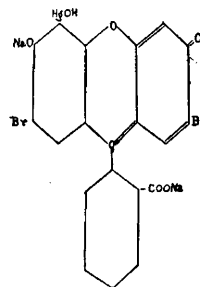
The irritating effect of solutions of mercuric chlorid is due to the mercury ion. If, however, the metal is substituted in an organic compound, such as an acid dye, the mercury no longer yields ions, but exists as a firmly bound part of the dye molecule itself. In this form of combination the properties of the metal as manifested by mercury salts are more or less completely masked. The new substance gives a negative reaction with the usual reagents for mercury, such as alkalis, iodids and alkali sulphids. The organic combinations of mercury also generally exhibit lower toxicity than do corresponding amounts of mercury in salt form, and frequently, but not always, their germicidal action is milder than that shown by the salts. With the great variety of possible combinations offered, depending on the nature of the organic substance used, it is not very difficult to find products whose advantages of nonirritability, lower toxicity and high penetrating power more than offset their somewhat decreased germicidal power as compared with that of the mercury salts.

Although a large amount of investigation of the therapeutics of the organic mercury compounds has been carried out in Europe, the study of these compounds in this country has, as far as we know, been limited to that of Davis, White and Rosen<sup>5</sup> and of Schamberg, Kolmer and Raiziss.<sup>6</sup> Most of the work abroad has dealt with the use of these substances in trypanosome infections. The principles we employ in the use of organic mercury compounds in the urinary tract we believe are new.

#### DESCRIPTION OF MERCUROCHROME-220

To the substance obtained by substituting one atom of mercury in the molecule of dibromfluorescein we have given the name "mercuochrome-220."<sup>6</sup> Chem-

ically it is dibrom-oxymercuryfluorescein, or its sodium salt. The latter contains about 26 per cent. of mercury, and is represented by the formula:



The free acid is a red powder insoluble in water but readily soluble in sodium hydroxid solution, with the formation of a deep cherry red color, showing fluorescence on dilution. The dry salt forms iridescent green scales, slightly hygroscopic and readily soluble in water. The solution is stable and is not affected by moderate heat or exposure to the air. Strongly acid urine ( $p_H=5.0$ ) gives a slight precipitate of the free dye; but if the acidity is  $p_H=6.4$  or less, no precipitation occurs. There is entire freedom from precipitation when a 1 per cent. solution of the drug is mixed with an equal volume of medium rich in protein, such as hydrocele fluid. The solution stains the skin a bright red color, but the stain is readily removed by rubbing first with 2 per cent. potassium permanganate solution, and then with 2 per cent. oxalic acid solution.

It was found that under proper conditions a second atom of mercury could be introduced into the dye molecule. However, the substance thus formed showed no greater germicidal action than the simpler compound, and was consequently discarded.

It should be mentioned that a "mercury dibromfluorescein" has been experimented with by Hahn and Kostenbader.<sup>7</sup> These authors give no description of their drug, but its mercury content (35 per cent.) indicates that it differs from our substance and that it is not a homogeneous chemical compound.

#### PENETRATION

Attention must be paid to the penetrating power of any germicide for use in the urinary tract. Fenger<sup>8</sup> has shown that "in thirty-eight hours after inoculation the gonococci have only just begun to effect entrance between the epithelial cells. The inflammation extends until the gonococci have penetrated deep into the layers of the mucous membrane, which has become acutely congested, the epithelium undergoing mucous degeneration, and exfoliating in patches." MacCallum<sup>9</sup> states that "the gonococcus penetrates among the epithelial cells and extends even into the subepithelial tissues of the urethra." Sections made from cases of papillary cystitis and from pyelitis show the organisms to have penetrated to the deeper layers of the epithelial cells.

Attention was called by Davis and Harrell<sup>4</sup> to the rapid diffusibility of acriflavine in the tissues. During the administration of mercuochrome-220 by injection of solutions into a rabbit's ear vein to determine toxicity, the same phenomenon was observed. This compound spread rapidly from the vein into which it was being injected, and in a few seconds the entire ear

5. Schamberg, J. F.; Kolmer, J. A., and Raiziss, G. W.: A New and Superior Mercurial Germicide, *J. A. M. A.* **68**:1458 (May 19) 1917. Schamberg, Kolmer, Raiziss and Trist: *J. Infect. Dis.* **24**:547 (June) 1919.

6. The name "mercuochrome" will be applied generically to all the mercury-bearing dyes that we are investigating, the individual being distinguished by the laboratory number following the name. We have made a number of such compounds, including phthaleins, azo dyes, basic dyes, thiazins, etc., on which we shall report in due time.

7. Hahn and Kostenbader: *Ztschr. f. Chemotherap.*, Orig., **2**:71, 1914.

8. Fenger, quoted by Keyes: *Modern Urology*, **1**:59.

9. MacCallum: *Textbook of Pathology*, p. 530.

was colored a reddish pink. This color persisted with varying intensity for from twenty-four to forty-eight hours.

With a view to determining the penetrability of this mercury-bearing dye, when used in the urinary tract, a series of direct experiments was carried out. A rabbit was catheterized, a soft rubber catheter being used. Through this catheter an ounce of 1 per cent. solution of the drug was slowly injected into the bladder, and the catheter was slowly withdrawn, allowing some of the fluid to escape through the urethra. At the end of five minutes the catheter was again introduced, and the bladder was emptied. The rabbit was quickly killed, and the bladder and urethra were dissected out intact. The bladder was then opened, and excess of solution was removed by washing with water. Frozen sections of the urethra and bladder were made immediately and were examined without the use of any other stain. In other instances the bladder and urethra were opened and immediately transferred to formaldehyd solution and hardened. Paraffin blocks were made and sections were cut without the use of any other stain. This experiment was carried out several times, the catheter being used in one instance, and in the other instances the bladder being filled through the urethra by means of a small syringe. The latter method was used to avoid any possible trauma to the urethral mucosa. In other rabbits under ether anesthesia, the abdomen was opened, the ureters were exposed, and by means of a small record syringe the ureter and kidney pelvis were gently filled with a 1 per cent. dye solution, care being taken to prevent overdilatation of the kidney pelvis, and the ureter was ligated. After five minutes the rabbit was killed, the ligature was removed from the ureter, the kidney and the ureter were taken out intact, and frozen sections were made and promptly examined. In other instances, paraffin sections were made.

Examination of the frozen sections as well as of the paraffin sections shows that the epithelial cells of the urethra are stained a deep red. This staining is most intense in the superficial layers, and becomes less intense toward the submucosa; but the submucosa was stained in places, though not so uniformly as the epithelial layers. In some places the stain penetrated the submucosa into the muscularis. This mercury-bearing dye stains the epithelium of the anterior and posterior urethra uniformly, and to a less extent penetrates to the submucous layers. Sections of the bladder and the ureter show the same uniform penetration and staining of the cytoplasm of the epithelial cells, and the submucosa is less deeply stained. Sections of the kidney pelvis showed penetration and staining of the epithelium. The dye had also been taken up by the cells of the collecting tubules, and they were stained for a short distance up the tubules from the papillae. In the urethra, the epithelium of the glands opening into the urethra was stained for some distance from the mouths of the ducts.

#### TOXICITY

In determining the toxicity of the drug, various solutions were administered intravenously. The urine was examined and the phenolsulphonephthalein excretion was determined, and in dogs blood urea was determined before injection. We noticed a variation in the amount of the drug that rabbits and dogs could tolerate. Ten mg. per kilogram invariably killed rabbits in

twenty-four hours, and no gross lesions were found at necropsy. Rabbits receiving 5 mg. per kilogram showed a decrease in phenolsulphonephthalein output and an albuminuria that lasted about a week. Dogs tolerated 10 mg. per kilogram very well with no evidence of discomfort or illness. In each instance there was produced an albuminuria without casts and a temporary reduction in phenolsulphonephthalein output but no rise in blood urea. The albuminuria persisted about five days. At no time were casts found. The phenolsulphonephthalein output returned to normal with the disappearance of the albuminuria. No evidence of kidney damage was found at necropsy on animals killed at the end of the experiments. With this toxic limit established no harm is to be expected from the small amount of the drug that may be absorbed when used locally in the genito-urinary tract.

#### IRRITATION

One per cent. solutions of mercurochrome-220 gave no evidence of irritating qualities when used in the conjunctival sac of rabbits. Solutions of this drug in strength from 0.1 to 5 per cent. have been used in the human genito-urinary tract as a local antiseptic. In the kidney pelvis a 1 per cent. solution was used. This was slowly injected through the ureteral catheter, the catheter was plugged, and the solution was retained for five minutes. There has been no sign of irritation or reaction following its use. This procedure has been carried out three times in one week in some instances. In the urethra a 5 per cent. solution caused only temporary burning when retained five minutes, and a number of cases of acute urethritis have been treated by the use of 1 per cent. solution injected four times a day, the solution being retained five minutes at each injection. There has been no irritation beyond occasional temporary smarting. No cases of retention have been seen, and no stricture formation has resulted from its use in our series of cases, as will be seen from the case reports.

In only two instances was there any complaint of burning or irritation. These were both chronic cystitis cases in old men with residual urine. One of them had extensive carcinoma of the prostate involving the bladder, with a residual urine of 200 c.c. He was on interval catheterization, and about 1 ounce of 1 per cent. mercurochrome was placed in the bladder and retained until the next catheterization, about six hours later. This man complained of severe burning in the bladder and had a reaction, which persisted for several days, after which his urine became much clearer but his infection persisted. The other case was similar, that of an old man with an enlarged prostate, his general condition being such as to make prostatectomy out of the question. There were several hundred cubic centimeters of residual urine. After several hours he complained of severe burning in the bladder, which persisted several days.

With the exception of the two cases noted, we have seen no irritation beyond occasional temporary smarting at the time of injection. The solution has been used in a number of bladder infections with small amounts of residual urine without irritation. The fact that irritation has been seen so rarely indicates that its occurrence in these cases is due to some individual hypersensitiveness rather than to any inherent property of the drug. Some observers who have been using

it have reported not only absence of irritation but also a prompt cessation of pain following the use of the drug in infected bladders and kidney pelves.

#### BACTERIOLOGIC TECHNIC

The medium chosen in which to test the germicidal action of drugs intended for use in the urinary tract was urine. We are aware that the objection may be raised that many infections have their seat in an environment more closely related to serum than to urine, and that serum therefore represents the most rational medium for test tube experiments. How far this contention really applies to infection of the urinary tract may well be questioned, especially in such infections as may be located not much deeper than the epithelial layers. Moreover, no set of test-tube experiments can be relied on for much more than a rough comparative evaluation of various germicides, which will bear no necessary relation to relative efficiency in clinical tests. For this reason urine seemed a medium fairly well representing clinical conditions. It had the further advantage that the results obtained with it take into account any precipitation or other chemical change that the drug may undergo under conditions of actual clinical application in the urinary tract.

The tests were carried out after this manner: Urine was voided aseptically into sterile flasks, and adjusted to the reaction of 6.4 on the hydrogen-ion scale. Blank tests were made to insure sterility. Nine c.c. of this urine were inoculated with a 3 mm. loopful of a twenty-four hour broth culture of the organism. To the inoculated urine was added 1 c.c. of an aqueous solution of the drug ten times as strong as was desired in urine dilution. Thus, 9 c.c. of urine plus 1 c.c. of the 1:100 drug solution gave a final dilution of 1:1,000 in urine. The mixture was at once well shaken, and at the end of the desired time period 0.1 c.c. of the mixture was transferred with a sterile capillary pipet to 10 c.c. of agar, and this mixture was immediately plated. The advantage of adding the drug to inoculated medium rather than to inoculate medium already containing the drug has been forcibly pointed out by Dakin and Dunham.<sup>10</sup> The former procedure simulates that carried out in an actual disinfection, and has the advantage that, in case the drug is altered in any way by the medium, it at least gets an equal chance to act on the organisms as well as be acted on by the medium.

In making tests with final dilutions that are low (for example, 1:100), it must be remembered that a considerable concentration of the drug may be present in the agar plate. Thus, if 0.1 c.c. of a 1:100 solution in urine be transferred to 10 c.c. of agar, we shall have a new hundredfold dilution; that is, the dilution in agar will be 1:10,000. Since the agar plate is incubated at least twenty-four hours, we have in effect action of a 1:10,000 solution on the organism for twenty-four hours rather than action of a 1:100 solution for whatever time period we may choose in our test. The results thus obtained are obviously erroneous, and in order to avoid them, this expedient was adopted: After the low dilution (1:100) had acted on the inoculated urine for the stipulated time, 0.1 c.c. was mixed with 2 c.c. of sterile water, and 0.1 c.c. of this new dilution was plated with 10 c.c. of agar. The dilution in agar was then 1:200,000, a dilution which separate experiments showed was without action on

the organisms even in twenty-four hours. Blank experiments with this double dilution showed that when no drug was present, enough organisms were left to give a good growth in agar plates.

The composition of urine from the same individual varies considerably, and of course variable results were obtained. In every case three or more tests were made, and the figures given in the tables represent the highest dilution that always gave a sterile plate. In all cases an average of results would be more favorable to the drug, but we feel that the method of report we have adopted is safer and less open to criticism than an average would be.

In testing the germicidal value of the flavines, the precaution must be taken to read the plates after forty-eight hours as well as after twenty-four hours. We have frequently found that a flavine plate would apparently be sterile at the end of the first period and would show a growth of many colonies at the end of the second period. No such delayed growth was observed in tests with mercurochrome-220. This emphasizes the fact that the value of the flavines lies in their antiseptic action rather than in their germicidal action.

It should be mentioned that the notable difference between the action in acid and in alkaline urine shown by acriflavine is not shown by mercurochrome-220. The action shown by this compound in alkaline urine was slightly inferior to that shown in slightly acid urine.

#### COMMENT ON BACTERIOLOGIC TESTS

The outstanding fact observed on comparing the germicidal values of mercurochrome-220, acriflavine, protargol and argyrol (Tables 1, 2, 3, 4 and 5) is the *rapidity* of action of the mercury compound in fairly high dilutions. In one minute it kills *B. coli* or *Staphylococcus aureus* in a dilution of about 1:1,000, a result obtained with none of the other drugs even in one hour. In fifteen minutes its effect is nearly as great as in twenty-four hours, killing *B. coli* in this short time at 1:5,000, and *Staphylococcus aureus* at 1:10,000. A few tests were made to learn the minimal time in which a 1:100 solution would sterilize. *Staphylococcus aureus* was killed almost instantaneously; that is, as rapidly as we could introduce the drug, withdraw a sample, dilute in water (to dilute the drug out of action in the agar) and plate. *This procedure took no longer than ten seconds.* The same test on *B. coli* revealed that a few organisms remained after ten seconds' exposure to the drug. Since a 1:800 solution kills this organism in one minute, the time necessary for a 1:100 solution to kill is possibly no more than thirty seconds.

Acriflavine is shown to be much less potent as a germicide in even the most concentrated solutions, if allowed to act on the organisms for one hour or less. It surpasses mercurochrome-220 in the twenty-four hour test, at this time period appearing to be about four times as effective as the mercury compound. It is hardly logical to judge a local urinary germicide by its action on organisms during such a long period of time; a short period of exposure in the test, on the other hand, approximates clinical conditions. If *rapid* disinfection is a desideratum, as it appears to be, mercurochrome-220 is superior to acriflavine.

Comparison of mercurochrome-220 with the silver protein compounds is open to two interpretations. If we consider the action in the test tube of those solu-

10. Dakin and Dunham: Brit. M. J. 2: 641 (Nov. 17) 1917.

tions used clinically—10 per cent. argyrol and 1 per cent. protargol—the silver compounds compare favorably with the mercury dye except in the action of

TABLE 1.—THE GERMICIDAL STRENGTH OF MERCUROCHROME-220 IN URINE \*

Medium	Organism	Time Exposed to Drug	Highest Dilution Killing Uniformly	
Urine (pH = 6.4)	B. coli	1 minute	1 : 800	
	S. aureus	1 minute	1 : 1,000	
	B. coli	5 minutes	1 : 1,000	
	S. aureus	5 minutes	1 : 5,000	
	B. coli	15 minutes	1 : 5,000	
	S. aureus	15 minutes	1 : 10,000	
	B. coli	1 hour	1 : 5,000	
	S. aureus	1 hour	1 : 10,000	
	B. coli	24 hours	1 : 20,000	
	S. aureus	24 hours	1 : 20,000	
	Hydrocele fluid	B. coli	1 hour	1 : 1,000
		S. aureus	1 hour	1 : 1,000
B. coli		24 hours	1 : 4,000	
S. aureus		24 hours	1 : 4,000	

\* The test consisted in treating 9 c.c. of sterile urine with 1 c.c. of drug solution ten times as strong as desired in final urine dilution. One-tenth c.c. portions were placed in agar at the end of stipulated periods.

protargol on *Staphylococcus aureus*. If, on the other hand, we consider the action of solutions of the same concentration of these three substances, we find that the silver compounds are in no wise comparable with mercurochrome-220. Since most of the urinary infections penetrate more or less deeply into the mucosa, therapeutic results will probably be controlled by the concentration of the germicide that finds its way into the tissues. It therefore appears that our comparison should take into account the effective concentration of the various drugs, rather than the concentrations applied to the surface of the infected area. The latter concentrations may not, and in the case of a nonpenetrating substance, like argyrol or protargol, probably do not, represent the relative concentrations of the germicide actually reaching the seat of the infection.

TABLE 2.—THE GERMICIDAL STRENGTH OF ACRIFLAVINE IN URINE \*

Medium	Organism	Time Exposed to Drug Action	Highest Dilution Killing Uniformly
Urine pH = 6.4	B. coli	1 hour	1 : 100
	Staph. aureus	1 hour	1 : 200
Urine pH = 7.6	B. coli	1 hour	1 : 200
	Staph. aureus	1 hour	1 : 400
Urine pH = 6.4	B. coli	24 hours	1 : 10,000
	Staph. aureus	24 hours	1 : 60,000
Urine pH = 7.6	B. coli	24 hours	1 : 70,000
	Staph. aureus	24 hours	1 : 80,000

\* No exposure for less than one hour was made because of the weak germicidal action for the one hour period.

For this reason a comparison of absolute concentrations (Table 5) seems a reasonable one, in view of the superior penetrating power of mercurochrome-220, and such a comparison shows a superiority of the mercury dye over the silver proteins. Thus, whereas both argyrol and protargol at 1:1,000 fail to kill either *B. coli* or *Staphylococcus aureus* in one hour, the same concentration of the mercury dye kills both organisms in about one minute.

METHODS EMPLOYED IN THE CLINICAL USE OF MERCUROCHROME-220

In the treatment of infections of the kidney pelvis, the following procedure was employed: Ureteral catheterization was done and a separate collection was made from each kidney. This was centrifuged, and a stained smear was made and examined microscopically. After the collection was completed, the kidney pelvis was gently filled, the gravity method being used in

some instances and the syringe in others, with a 1 per cent. solution of mercurochrome-220, the catheter being plugged and the fluid retained in the pelvis for five minutes. There has been no complaint of pain and no severe reaction in any of our cases. This procedure was repeated twice a week, and when the urine from each kidney was free from pus and organisms for a week, the patient was discharged to return for further observation in a month.

In treatment of bladder conditions, the urethra was first irrigated with sterile water, a coudé catheter was passed, and the bladder was washed clean. One ounce of 1 per cent. mercurochrome-220 was then injected into the bladder through the catheter by pressure from a bulb syringe, or by a Keyes syringe. The patient was instructed to retain this solution for at least one hour, and longer if possible. Some patients have been able to retain the solution for more than three hours. This procedure was carried out twice a day, as a rule, and in some instances three times a day. There was

TABLE 3.—GERMICIDAL STRENGTH OF ARGYROL, 10 PER CENT. SOLUTION, IN URINE

Time of Exposure	Organism	Result
5 minutes	B. coli	No growth
5 minutes	S. aureus	No growth
15 minutes	B. coli	No growth
15 minutes	S. aureus	No growth
1 hour	B. coli	No growth
1 hour	S. aureus	No growth

TABLE 4.—GERMICIDAL STRENGTH OF PROTARGOL, 1 PER CENT. SOLUTION, IN URINE

Time of Exposure	Organism	Result
5 minutes	B. coli	No growth
5 minutes	S. aureus	Growth
15 minutes	B. coli	No growth
15 minutes	S. aureus	Growth
1 hour	B. coli	No growth
1 hour	S. aureus	Growth

occasionally some slight burning and smarting, which lasted only a short time. Several complained of smarting of short duration after three or four treatments, but not at first. The urine voided by the patient on arising in the morning was centrifuged. A stained smear was made and examined. After three or four treatments, the urine usually began to clear up, and as soon as it was free from organisms, the number of treatments per day was gradually reduced. It was noticed that as long as mercurochrome-220 was used in the bladder, the urine remained hazy owing to the

TABLE 5.—GERMICIDAL STRENGTH OF ARGYROL AND PROTARGOL IN URINE, pH = 6.4

Drug	Organism	Time of Exposure	Highest Dilution Killing the Organism
Protargol	B. coli	1 hour	1 : 1,000 failed
	S. aureus	1 hour	1 : 1,000 failed
	B. coli	24 hours	1 : 2,000
	S. aureus	24 hours	1 : 2,000
Argyrol	B. coli	1 hour	1 : 1,000 failed
	S. aureus	1 hour	1 : 1,000 failed
	B. coli	24 hours	1 : 1,000 failed
	S. aureus	24 hours	1 : 1,000 failed

presence of exfoliated epithelial cells, and not of pus and organisms.

An abstract of ten cases treated in this clinic is included herewith.

REPORT OF CASES

CASE 1 (F-32830, J. H. H. D., Dr. Wesson).—*Urethral stricture, periurethral abscess, cystitis and posterior urethritis.*

—A white man, aged 54, came in complaining of inability to void urine. The family history was negative. The patient denied previous venereal disease. Four years before, the patient was admitted to the Johns Hopkins Hospital with a diagnosis of perineal abscess and urethral stricture. During his stay of one month in the hospital, the abscess was opened and the stricture was thoroughly dilated. During the interval the patient had no trouble. On his return there was a large swelling in the perineum, and the patient voided with great difficulty. Filiforms and followers up to 24 F. were passed, and a coude catheter was then introduced, through which 500 c.c. of foul-smelling, sanguinopurulent urine was withdrawn. The patient was placed on daily bladder irrigations of a potassium permanganate solution (1:6,000) and at the end of five days the urine was still cloudy and infected with both bacilli and cocci. Irrigation of a warm solution of mercurochrome-220 (1:1,000) were then given daily. Following the irrigation, 1 ounce of 1 per cent. mercurochrome-220 was placed in the bladder and the patient was instructed to retain this for at least one hour. The infection immediately began to clear up, and at the end of five days the urine was clear and entirely free from pus and organisms, and remained so until his discharge from the clinic four weeks later. The patient is still under observation, returning for weekly dilations of the stricture. The patient was able to retain the 1 per cent. mercurochrome-220 solution for more than two hours in the bladder without any discomfort.

CASE 2 (7298, B. U. I.).—*Subacute cystitis with chronic seminal vesiculitis*.—A white man, aged 20, came in complaining of the presence of pus in the urine. The family and venereal histories were negative. The patient stated that for the past three years he had had intervals of bladder irritability associated with the passage of cloudy urine. The past history was otherwise negative. Examination of the urine disclosed the presence of a bacillus infection and a large amount of pus. Ureteral catheterization repeated several times revealed that the kidneys were free from infection, and no acid-fast organisms were ever found. The patient received treatment at irregular intervals at the Brady Clinic for six months, receiving prostatic massage, seminal vesicle stripping, irrigations with potassium permanganate solutions (1:1,000), and instillations of solutions of acriflavine (1:1,000). Flavine solutions were used twice a week for two months without clearing up the infection. Instillations of from one-half to 1 ounce of 1 per cent. solution of mercurochrome-220 were then begun, given on alternate days. The urine began to clear immediately, and after the sixth treatment was found to be free from pus and organisms. The urine was examined at weekly intervals for a month, and no infection was found at any time. The patient had no difficulty in retaining the solutions in the bladder for from one to three hours. The patient returned, after a month's absence, with cloudy urine, which was found to be due to phosphates and was free from infection and pus.

CASE 3 (7775, B. U. I.).—*Cystitis*.—A white man, aged 54, came in complaining of kidney trouble. The family and venereal history were negative. He gave a history of a severe left-sided renal colic twenty years previously. He had had no recurrence or symptoms until six months before, but had had about a dozen attacks in the past six months. On admission his bladder urine was cloudy, owing to a small amount of pus and a bacillus infection. The duration of this infection was indefinite. On cystoscopy there was no residual urine, and the bladder capacity was 250 c.c. The bladder was trabeculated, and a small median bar with a pouch behind it existed. The kidneys were negative and no stone was found in either the ureter or the kidney by wax tip, plain roentgen ray or pyelogram. The treatment consisted of daily instillations of one-half ounce of 1 per cent. mercurochrome-220 through a posterior urethral instillator into the empty bladder, the patient retaining the solution for at least an hour and for longer periods if possible. After the first injection, the urine became clearer, but pus cells and organisms persisted until the fourth treatment. After this the urine contained a few desquamated epithelial cells, but no organisms were found at any time. The urine was studied twice during the

week following the discontinuance of treatments and was found free from infection both times, and also on discharge at the end of this time.

CASE 4 (6607, B. U. I.).—*Bilateral pyelitis and cystitis*.—A white man, aged 58, came in complaining of soreness in the left kidney region. This was the patient's third admission to the hospital. On his first admission he had a perineal prostaticectomy, convalescence from which was satisfactory except for a complicating epididymitis, and a febrile reaction associated with a pain in the lumbar region, probably due to a pyelitis. The patient improved markedly after leaving the hospital, and was well up to five weeks previous to his second admission. At this time he noticed that the urine was cloudy and highly colored. Three weeks previous to this he had had a second febrile reaction associated with pains in the kidneys. Ureteral catheterization disclosed a bacillary infection of both kidney pelvises. The patient was treated by pelvic lavage, silver nitrate solutions being used and his infection entirely cleared up, so that on his discharge he had no pus or organisms in the urine. At this time he developed an acute epididymitis, which prolonged his convalescence. Four months later he returned to the hospital the third time, and a diagnosis of bilateral pyelitis and papillary cystitis due to a bacillus was made. The pyelitis was treated by pelvic lavage, 1 per cent. mercurochrome-220 solutions being used. The pelvis was gently filled with the solution until the patient became conscious of a sense of distention; the catheter was then withdrawn, leaving the pelvis filled. This was done once a week, and on alternate days the bladder was treated. From one-half to 1 ounce of a 1 per cent. mercurochrome-220 solution was used, being injected into the empty bladder and retained for an hour or more. It required ten treatments to render the urine pus-free and organism-free. The patient's urine was free from pus and infection on discharge after one month's treatment.

CASE 5 (7498, B. U. I.).—*Prostatic bar obstruction; Cystitis and bilateral pyelitis*.—A white man complained of pain across the pubic region on admission. The family history was negative except for the death of one brother from tuberculosis. He admitted a gonorrhoeal infection twenty years previously with no complications or recurrences. He dated his trouble to a severe attack of influenza about one year before. On his first admission to the hospital, studies made then led to the diagnosis of cystitis, median bar obstruction, bilateral pyelitis due to a bacillus infection, and a right-sided hydronephrosis of moderate grade. Previous to his admission the patient had been treated in another hospital for seven weeks by pelvic lavages, autogenous vaccines and bladder irrigations, but the infection persisted.

On his second admission a punch operation was done. When convalescent, ureteral catheterization was performed, and the urine from both kidneys was found infected with bacilli, there being only a few pus cells present. Each pelvis was filled by gravity with a 1 per cent. mercurochrome-220 solution, and the catheter was withdrawn. Examination of the urine obtained by ureteral catheterization on the first and third days following this one treatment failed to reveal any pus or organism. The patient left the city immediately after this last examination, but at a later date is to report for observation.

CASE 6 (E, outside case).—*Cystitis*.—A white man, aged 35, came in for an examination because of cloudy urine. The family and personal history were negative. The patient's urine was found to contain a small amount of pus and many bacilli. No definite history as to the length of time the infection had existed could be obtained. The kidneys were negative on ureteral catheterization. No pathologic condition was found in the bladder except signs of a chronic cystitis due to long-standing infection. Daily instillations of one-half ounce of 1 per cent. mercurochrome-220 were carried out, and on the fourth day the urine was found to be free from infection and pus, and remained clear until the patient left the clinic.

CASE 7 (7728, B. U. I.).—*Prostatic bar; cystitis*.—A white man, aged 53, came in complaining of prostate trouble. The family and personal histories were negative except for two

gonorrhoeal infections without complications. On admission the patient had a few cocci in his bladder urine but no pus cells. Cystoscopy revealed a prostate bar, and a punch operation was done and a retention catheter was left in place for forty-eight hours. On the removal of the catheter the urine was found to contain a large amount of pus, many bacilli and no cocci. The patient was treated by instillations of from one-half to 1 ounce of 1 per cent. mercurochrome-220. These treatments were preceded by irrigation of the anterior urethra; a coudé catheter was then passed, and the bladder was irrigated with sterile water. Instillations were given twice a day, and the solution was retained for at least an hour without any pain or burning. After the first day the urine became clearer, and after seven instillations (the morning of the fourth day) the urine was found to be free from organisms. Daily examination of the first urine voided in the morning failed to detect any infection during his subsequent stay of one week at the clinic.

CASE 8 (4364, B. U. I.).—*Chronic cystitis*.—A white man, aged 68, came back for observation. The patient had had a perineal prostatectomy four years previously, and had secured an excellent result; but a bladder infection persisted. Examination of the urine revealed a large amount of pus and many bacilli. The urethra was thoroughly irrigated with sterile water; a coudé catheter was passed; the bladder was washed clean with sterile water, and 1 ounce of 1 per cent. mercurochrome-220 was injected through the catheter into the bladder. This was done twice a day. Daily examination of the urine was made. The morning urine the third day (after five treatments) was found to be free from organisms, but contained many epithelial cells. The urine was examined each day during the rest of his stay at the clinic (three days), and no organisms were found at any time. There was no irritation or burning when the solution was retained in the bladder from two to three hours.

CASE 9 (7732, B. U. I.).—*Chronic cystitis*.—A white man, aged 53, complained of kidney trouble. The family and personal histories were negative. For the past three years the patient had had a pain in the right lumbar region at times. This was never severe, but rather of the dull aching character. Five months before admission, the patient began to have hematuria and renal colic on the right side. Ureteral catheterization revealed a coccus infection on the right side and no infection on the left side. A pyclogram was made and a diagnosis of right hypernephroma made. Nephrectomy was performed. Following this the bladder infection persisted. The patient was then given bladder instillations of one-half ounce of 1 per cent. mercurochrome-220 on alternate days to be retained for one hour. There was an immediate reduction in the number of pus cells and organisms. After the seventh treatment the urine was found to be free from infection and remained so for two weeks. In this time the urine was carefully examined four times, but no infection was found.

CASE 10 (7857, B. U. I.).—*Cystitis*.—A white man, aged 50, had complained of urinary difficulty for the past six years. The family and personal histories were negative except for two gonorrhoeal infections, the last one being six years previously, from which time the patient dated his urinary trouble. Examination detected a tight stricture in the membranous urethra and a contracted vesical orifice. A punch operation was done under local anesthesia, and a retention catheter was left in the bladder for drainage for forty-eight hours. The patient developed a mixed infection of the bladder, both bacilli and cocci together with a large amount of pus being found in the urine. After the removal of the tube, daily instillations of 1 per cent. mercurochrome-220, preceded by irrigations of sterile water, were begun. The urine was examined daily. There was a gradual diminution in the number of organisms and the amount of pus. There were no organisms found on the fifth day, a very few on the sixth and none afterward up to the twelfth day of the treatment.

#### RESULTS IN URETHRITIS

The bacteriologic tests of the action of mercurochrome-220 on the gonococcus have not been completed as yet and will be published later.

In fifty-one cases of acute specific urethritis, treatment has been given by intra-urethral injections of 1 per cent. solutions of this drug. These were all public dispensary cases, and a large number of the patients were negroes, many of whom failed to cooperate, while others failed to continue their treatment after the discharge began to diminish, especially if they had no complication to cause them pain or annoyance. In none of these cases have we seen any irritation beyond a temporary burning or smarting, whether the drug was used in the anterior or in the posterior urethra.

The method used in these cases has been: microscopic diagnosis as to the presence or absence of gonococcus; the three glass test to determine the part of the urethra involved and the extent of involvement, and an examination of the prostate and the vesicles on the first visit. We did not examine the urethra with a bougie à boule, owing to the presence of an acute discharge. An anterior urethral irrigation of warm sterile water or dilute (1:10,000) potassium permanganate solution was then given. This was followed by the careful injection into the anterior urethra of sufficient 1 per cent. mercurochrome-220 solution to fill completely the anterior urethra, the patient compressing the lips of the meatus and retaining the solution for five minutes. If the posterior urethra was involved, the solution was gently forced into the posterior urethra by means of a bulb syringe, and was retained in the bladder for an hour or more. A small quantity of the drug solution and a blunt nosed urethral syringe were dispensed, and the patient was instructed to inject the solution four times a day immediately after urinating, retaining it for five minutes. On return to the clinic, smears were examined microscopically, and as the organisms lessened in number, the number of injections was reduced to three and then to two and later to one per day. The reduction should be gradual. As long as the drug is used the urine will remain cloudy owing to exfoliated epithelial cells, which will be found stained pink, while the polymorphonuclear cells will not be stained by this drug.

We were able to follow thirty cases until an apparent cure was effected. This involved in some cases the treatment of preexisting or consequent prostatitis, vesiculitis or stricture. In such cases a cure was considered accomplished when the urethral discharge had disappeared and the urine remained free from shreds for two weeks. It was found very difficult to secure the cooperation of this class of patients, in the treatment of residual prostatitis, when all urethral and urinary signs had disappeared.

Twenty-one other patients were improved and discontinued treatment. The average length of time required to render the discharge free from gonococci was ten days. The shortest time required to accomplish this was three days. These were acute cases, two of which remained free from further infection, but in one case there was a recurrence of organisms after nineteen days, due to a reinfection from the prostate. The longest time required to render any case gonococcus-free was seventeen days. This was an acute exacerbation of a chronic infection, with involvement of the posterior urethra and the prostate.

Recurrence of organisms took place in six cases, or 20 per cent. of our total. Two of these six were cases in which the anterior urethra alone was involved, and the recurrence was probably due to stopping the injections before the entire canal had been sterilized.

Four of these recurrences were in cases having both anterior and posterior involvement. Epididymitis developed in two of these cases, and in one case strictures were found subsequently in the bulbous urethra.

The anterior urethra alone was involved in eighteen cases, or 60 per cent. of our series, there being anterior and posterior involvement in twelve cases, or 40 per cent., at the time the patients first presented themselves for treatment. Chronic prostatitis was found to be present in fifteen cases, or 50 per cent., on first examination. Three cases, or 10 per cent., developed com-

the polymorphonuclears predominate, and later the epithelial cells increase in number as the polymorphonuclears diminish. As the epithelial cells increase in number and the organisms disappear, the number of daily injections should be reduced gradually, taking about a week entirely to discontinue the drug. Any remaining catarrhal process in the urethra should be treated by the use of dilute potassium permanganate solutions (1:10,000) as a daily irrigation or silver nitrate 1:10,000. When the posterior urethra is involved, it frequently clears up before the anterior

TABLE 6.—CLINICAL RESULTS OF THE USE OF MERCUROCHROME-220 IN GONORRHEA

History Number	Age, Years	Previous Attacks	Days of Disease	Extent of Involvement				Mercurochrome-220, 1%		Gonococci													Day of Treatment to Free from Gonococci	No. of Days Free	Day of Recurrence	No. Days to Free from Gonococci after Recurrence	Complications and Remarks		
				Anterior	Anterior and Posterior	Prostatitis	Seminal vesiculitis	No. of daily Treatments	Irrigations	On Ad-mis-sion	Day after Admission																		
											3	4	5	6	7	8	9	10	12	Later									
F 5784	22	2	2	+	0	+	0	4	0	+++	++	..	++	..	..	..	0	..	..	0	..	0	7	27	0	..	Prostatitis present on admission		
F 9622	29	4	30?	+	0	+	0	3	0	++	+	..	0	..	..	..	0	..	..	0	..	0	5	?	0	..	Prostatitis present on admission		
F 87484	23	1	14?	+	0	+	0	3	0	+++	0	..	0	..	0	..	..	..	..	0	..	..	5	15	15	7	Recurrence due to prostatitis		
G 13960	32	0	7	+	0	0	0	3	0	+++	+	..	0	..	..	..	0	..	..	..	..	..	5	?	..	..	Discontinued treatment after ten days		
G 8731	22	0	5	+	0	0	0	4	+	+++	++	..	..	+	..	+	..	++	++	0	16	8	..	..	..	..	Discontinued treatment after eight days		
G 10196	34	4	60?	+	+	+	+	3	+	++	++	..	..	+	..	0	..	..	..	..	..	9	..	0	..	..	Complications treated three weeks		
G 9522	23	1	5	+	0	0	0	3	0	++	..	0	..	..	0	..	..	..	..	..	..	4	12	12	..	..	Discontinued treatment		
G 13733	20	1	21	+	0	0	0	4	0	++	+	..	..	+	..	..	0	..	..	..	..	9	5	..	..	..	Did not return for examination		
G 8924	28	1	7	+	0	0	0	3	0	++	..	+	..	..	++	..	+	..	+	+	0	14	..	..	..	..	..	..	
B 7681	20	1	120	+	+	+	+	4	+	+++	..	+	..	..	..	+	..	+	+	0	12	21	0	..	..	..	..	Slight prostatitis on discharge	
G 9824	28	1	7	+	0	0	0	3	0	+++	..	+	..	..	++	..	+	..	+	0	12	..	0	..	..	..	..	..	
G 8875*	22	2	10 mo.	+	0	0	0	4	+	+++	..	+	..	..	++	..	+	..	+	0	12	20	20	7(?)	..	..	..	Recurrence due to anterior stricture	
G 10291	24	0	7 mo.	+	0	0	0	3	0	+++	..	+	..	..	..	..	++	..	+	..	0	14	?	..	..	..	..	..	Posterior urethritis; prostatitis; epididymitis on sixteenth day
GS 5669	25	0	Days 4	+	0	0	0	4	0	+++	..	+	..	..	..	..	0	..	..	..	..	8	42	0	..	..	..	Reexamined six weeks later; cured	
G 7260	30	0	5	..	+	+	0	4	+	+++	..	..	+	..	..	+	..	+	..	+	0	14	15	0	..	..	..	Reexamined two weeks later; cured	
G 6907	23	0?	30	+	+	+	0	4	+	++	+	..	..	0	..	..	..	..	..	..	..	6	25	0	..	..	..	Prostatitis treated for twenty-five days	
G 7820	20	0	5	+	+	+	0	4	+	++	..	+	..	..	+	..	..	+	..	..	..	11	7	7	26	..	..	Prostatitis; recurrence due to stricture; dilated	
G 7920	21	0	21	0	+	+	0	3	+	+++	..	+	..	..	+	..	..	0	..	..	..	10	4	4	4	..	..	Prostatitis treated for sixty days	
G 8024	24	1	7	+	0	0	0	4	0	++	..	+	..	..	..	+	..	+	..	..	..	14	4	0	0	..	..	Colored; did not cooperate	
G 13860	22	1	7	+	0	0	0	4	0	++	..	+	..	..	0	..	..	0	0	0	..	7	5(?)	0	0	..	..	..	
G 12333	24	0	4	+	0	+	0	4	0	++	..	+	..	..	..	..	..	..	..	..	..	7	15	0	0	..	..	Few shreds in glass 1 two weeks later	
G 10816	26	0	7	0	+	+	0	3	+	++	..	+	..	..	..	+	..	..	..	..	..	11	?	0	0	..	..	..	
G 10863	22	0	15	0	+	+	0	3	+	+++	..	+	..	..	..	+	..	..	..	..	..	15	?	0	0	..	..	..	
G 11133*	29	5	?	0	+	+	+	3	+	+	0	..	..	..	..	..	..	..	..	..	..	3	14	0	0	..	..	Prostate and vesicles treated two weeks	
G 12144	27	0	30	+	0	0	0	4	0	++	0	..	..	..	..	..	..	..	..	..	..	3	19	19	4	..	..	Free from shreds in fifteen days	
G 91366	19	0	4	+	+	+	0	3	+	++	+	..	..	..	..	0	..	..	..	..	..	3	?	0	0	..	..	Prostatitis; seminal vesiculitis; epididymitis on ninth day	
G 6748	22	0	?	+	+	+	0	3	+	++	+	..	..	+	..	..	..	..	..	..	..	7	?	0	0	..	..	..	
G 13236	24	0	30	+	0	0	0	3	0	+++	..	+	..	+	..	..	0	..	..	..	..	10	?	0	0	..	..	..	
G 10733	23	1	21	+	0	+	0	4	+	++	..	+	..	..	+	..	..	..	..	..	..	9	20	0	0	..	..	Prostatitis treated for twenty days	
G 9031	21	1	90?	+	+	+	0	3	+	++	..	+	..	..	+	..	..	+	..	..	..	17	15	0	0	..	..	Prostatitis treated for two weeks	

\* Subacute; all others acute.

plications after treatment was begun. In two cases that were anterior when first seen, posterior urethritis and epididymitis developed, and in one, acute prostatitis and seminal vesiculitis were later complications.

In our series of cases there has been no irritation beyond temporary smarting at the time of injection. We have not observed the edema of the urethra and prepuce that is occasionally seen when other drugs are used. Following the first injections there is a slight increase in the amount of the discharge, which rapidly becomes mucopurulent, then serous as it diminishes in amount. With this change in discharge, the microscopic character of the discharge also changes. At first

urethra, in some instances only three or four injections being necessary to render the urine in the third glass clear. Care should be taken to eliminate reinfections from prostate and vesicles and urethral strictures by proper attention to these conditions when present.

The results obtained with mercurochrome-220 in gonococcal infections have been fairly uniform. The rapid disappearance of organisms in some cases has been striking. In others there has been more or less resistance to treatment. While our series is small, the results thus far obtained seem to us to warrant a more extended trial of this drug in these infections. The results are summarized in Tables 6 and 7.



CHANCROIDAL ULCERATIONS

As a result of the laboratory tests demonstrating the penetrability and germicidal activity of mercurochrome-220, it was decided to use it as a local application in the treatment of nonsyphilitic venereal ulcerations. Fourteen dispensary patients were treated with the local application of mercurochrome solutions. We were able to follow ten of these patients until healed. In four cases an initial treatment was administered and some of the solution was given for local use, but the patients failed to return for further treatment and observation. All these cases were negative on repeated dark field examination for *Spirochaeta pallida*, and gave negative Wassermann reactions. No cases are included in which the patients were found to be syphilitic or were receiving intravenous arsenical medication. The type of sore was that of the old sore with undermined edges and dirty gray necrotic base which showed no tendency to heal.

These sores were thoroughly cleaned with soap and water, and all the necrotic tissue was removed. A moist dressing of 1 per cent. mercurochrome-220 was then applied, and some of the solution was given the patient with instructions to moisten the dressings twice a day with the solution. Later it was found more convenient to use a starch paste containing 5 per cent. mercurochrome-220 by weight, instead of the solution, the sore being dressed only once a day. No irritation or burning was complained of by any of our patients.

TABLE 7.—SYNOPSIS OF RESULTS DETAILED IN TABLE 6

Number of cases studied.....	51
Number of cases observed until an apparent cure was effected.....	30
Number failing to improve.....	0
Minimum time required to render discharge gonococcus-free.....	3 days
Maximum time required to render discharge gonococcus-free.....	17 days
Average time required to render discharge gonococcus-free.....	10 days
Number of cases in which complications developed after treatment was begun.....	3

In all of the cases, the sores cleaned off in from one to four days and presented a healthy healing surface. The prompt change in the appearance of the lesions when treated with mercurochrome was very striking. After the sore was clean and healing over, a simple ointment of boric acid was used as a protective dressing, silver nitrate being used on the granulations as needed. Whenever indicated, a dorsal slit was made and buboes were opened and drained. Tables giving the length of time required for complete healing are not included, as many of the patients left the clinic after the sore was partly healed.

CONCLUSIONS

1. Mercurochrome-220 is experimentally a drug of great germicidal value, a solution of about 1:1,000 killing *B. coli* and *Staphylococcus aureus* in urine in one minute. It has practically fifty times the germicidal strength of acriflavine in urine medium for exposures of one hour.

2. In a strength of 1 per cent. the new drug is tolerated by the human bladder for from one to three hours without irritation. Injections of 1 per cent. solution into the renal pelvis are likewise free from pain, even when held in situ by plugging the catheter.

3. That mercurochrome-220 has a remarkable germicidal value is shown by the rapid sterilization accomplished in a series of cases of cystitis and pyelitis of long standing and refractory to other treatments. Now for the first time we feel that we have a method of quickly curing certain chronic infections of the bladder.

The rapidity with which a few cases of old purulent cystitis disappeared was surprising, becoming free of pus and bacteria in a few days.

4. Studies of the comparative value of acriflavine and mercurochrome-220 in gonorrhoea are not yet complete, but it has been demonstrated that with both drugs, methods of great value in the treatment of the disease have been produced.

5. Mercurochrome-220 has proved to be eminently satisfactory in the treatment of chancroids and as a dressing for buboes after incision.

Other drugs developed along the same lines have been produced and are being experimented with by us.<sup>11</sup>

ROENTGEN-RAY TREATMENT OF WIDE-SPREAD AND GENERALIZED DISEASES OF THE SKIN\*

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In the early days of the roentgen-ray therapy of skin diseases, those who resorted to this mode of treatment employed it chiefly in certain cutaneous affections which, as a rule, were restricted in area, or were limited to certain well defined regions of the body, or occurred only as circumscribed or isolated lesions. For example, such affections as epithelioma and sarcoma, the various granulomas, keloid, ringworm of the hairy surfaces, and other diseases which did not readily respond to the older methods of treatment in common use at the time, would be, so to speak, consigned to the mercies of the roentgen ray, to reap the benefits of, or to suffer the evils from a subtle and powerful therapeutic agent, the precise nature and action of which is to this day unknown. Even in such relatively small and well defined lesions as basal cell epitheliomas, keloids, warts and circumscribed granulomas, the administration of the roentgen ray was at one time, not far gone, a more or less haphazard, indeterminate process, the outcome of which, if it resulted favorably, was often at best only "the happy combination of fortuitous circumstances."

EXACTNESS IN THE ADMINISTRATION OF DOSAGE OF RAYS

As is well known, the last few years have witnessed great strides in the science and art of roentgenotherapy as applied to cutaneous affections. Improvements in the manufacture of the various types of exciting apparatus, and in devices for measuring the quality and quantity of the rays, have done much toward the introduction of many refinements in technic, so that we are enabled today to measure the exact quality and to determine the exact quantity of a given roentgen-ray

11. In treating acute anterior gonorrhoea, we are at present using a 25 per cent. solution of mercurochrome instead of 1 per cent. This may be used every three hours, and should be preceded by a cleansing irrigation of sterile water. It causes a little more burning than the 1 per cent. solution, which, however, is temporary. On incomplete data, it seems that the time necessary to render the urethra organism free is definitely shortened by the use of this stronger solution. No unfavorable complications have been observed. At present a series of cases is being treated by the use of 5 per cent. mercurochrome in lanolin, and petrolatum equal parts, instead of the starch paste. Incomplete results indicate that the lanolin ointment is as efficacious as the starch paste, and more easily prepared.

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