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THE TREATMENT OF SEPTICEMIA AND LOCAL INFECTIONS

BY INTRAVENOUS INJECTIONS OF MERCUROCHROME-220
SOLUBLE AND OF GENTIAN VIOLET*

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In our first paper on mercurochrome-220 soluble,¹ experiments were cited to show that it could be introduced intravenously in doses of 5 mg. per kilogram of body weight in rabbits and 10 mg. per kilogram in dogs, with impunity. In this paper we detailed a prolonged search which we had made with many old and new combinations of mercury and of dyes to find a germicide which would not coagulate albumin and was non-toxic. We showed that mercurochrome answered these requirements and could be used in wounds in a 1 per cent. solution. Our toxicity experiments were confirmed by Piper² on both animals and human subjects. His clinical results have been most striking. Later it was shown in our laboratories, by Hill and Colston³ that, after the intravenous administration of 1, 2.5, 5 and 10 mg. per kilogram of mercurochrome to normal rabbits, the urine became either bactericidal or strongly bacteriostatic for *B. coli*. This inhibitive action was strongest during the first five hours after injection. It was also shown that the increase in inhibitive action was not in direct proportion to increase in dosage, which can probably be explained by the fact that, with smaller doses, in rabbits from 1 through 5 mg. per kilogram, most of the drug is eliminated through the kidneys, whereas with higher doses there is diarrhea and intestinal elimination. The same authors⁴ have shown that, after the intravenous administration of mercurochrome to normal rabbits, the blood is strongly bacteriostatic for *B. coli* from fifteen through forty-five minutes after injection. In short, the direct action of mercurochrome is rapid: in the circulation, strongest the first hour, as is to be expected; in the urine, strongest the first five hours. Any indirect action

of the drug can be measured with difficulty, if at all, but it seems probable from the clinical cases cited here that such indirect action may exist. Before carrying out these later laboratory experiments we had decided to use mercurochrome intravenously.

REPORT OF CASES IN WHICH MERCUROCHROME WAS GIVEN INTRAVENOUSLY

CASE 1.—*General septicemia due to colon bacillus; patient almost moribund; condition cleared up by intravenous injection of 34 c.c. of 1 per cent. mercurochrome.*

H. A. D., a man, admitted, Dec. 30, 1922, complained of pain in the kidney. The present illness was of three weeks' duration, following grip. For two days the pain had been very severe, and, on examination, the kidneys were very tender. Urinalysis showed considerable pus, a moderate number of gram-negative bacilli, and a heavy growth of *B. coli-communior* on culture. Ureteral catheterization showed pus cells in a small amount from both kidneys, but no bacteria. On the following day the pain in the right kidney became aggravated, and the patient was admitted to the Johns Hopkins Hospital, Jan. 2, 1923, with a temperature of 103.4 F., pulse 124, and in a very toxic condition. Examination of the abdomen showed muscle spasm and tenderness in the region of the right kidney, and the diagnosis of right pyelitis was made. On the following day the patient's condition had become much worse; the temperature was still high, and the pulse very weak. The patient was irrational; there were purpuric eruptions on the neck, chest, abdomen and legs. Blood cultures showed a heavy growth of colon bacilli. The patient was seen, in consultation with the medical department; the diagnosis of general septicemia was confirmed, and the prognosis was apparently hopeless.

At this point, in conjunction with Dr. J. A. C. Colston, it was decided to inject mercurochrome intravenously in a dosage of 5 mg. per kilogram of body weight. The patient received 34 c.c. of 1 per cent. solution in the vein of the arm. The temperature rose to 104 F. at midnight, but in six hours had dropped to 97. The patient became rational in a few hours, and on the following morning his condition was marvelously transformed; the temperature was normal, and he said he felt quite well. A culture taken from the blood was sterile, and after that the patient continued to improve in strength. Subsequent cultures, January 5 and 8, also showed no growth. The patient was discharged from the hospital well on the 10th. When seen in October, 1923, his condition was excellent; the urine was sterile by culture.

This is the first case to be recorded of cure of colon bacillus septicemia by the intravenous injection of mercurochrome. The rapidity of restoration from imminent death to normal health was almost unbelievable.

The second case is one in which, at our suggestion, a similar treatment was given by Dr. Grantham, to whom we are indebted for the notes on the case.

CASE 2.—*Staphylococcus septicemia, and extensive subcutaneous abscesses following severe injury. Intravenous administration of mercurochrome; sterilization of blood and cure of local infection.*

A man, aged about 30, in previous good health, was injured in the region of the right shoulder by a circular saw. The

* From the Brady Urological Institute, Johns Hopkins Hospital.

* Read before the Southern Surgical Association, Dec. 11, 1923, and previously, in brief, before the Eighth District Branch of the New York State Medical Society, Oct. 4, 1923, and before the Southern Medical Association, Nov. 13, 1923.

1. Young, H. H.; White, E. C., and Swartz, E. O.: A New Germicide for Use in the Genito-Urinary Tract: "Mercurochrome-220," *J. A. M. A.* 73: 1483 (Nov. 15) 1919.

2. Piper, E. B.: The Treatment of Puerperal Sepsis by the Use of Mercurochrome, with a Report of Animal Experimentation of the Chemical Disinfection of the Blood, *Am. J. Obst. & Gynec.* 4: 532 (July) 1922.

3. Hill, J. H., and Colston, J. A. C.: A Note on the Bacteriostatic Action of Urine After the Intravenous Administration of Mercurochrome to Normal Rabbits, *Johns Hopkins Hosp. Bull.* 34: 220 (July) 1923.

4. Hill, J. H., and Colston, J. A. C.: A Note on the Effect of the Intravenous Administration of Mercurochromes on the Bacteriostatic Action of Blood, *Johns Hopkins Hosp. Bull.* 34: 372 (Nov.) 1923.

wound extended through the skin, muscles and the capsule of the joint, which was opened, and infection ensued. Following this he had an extensive cellulitis of the shoulder region, which extended to the chest, beneath the pectoral muscles, and also down the arm and beneath the tissues of the back. Dr. Grantham saw him about two weeks after the accident, at which time his condition was very bad. The temperature was 104, and he was delirious. The infection of the chest, back, shoulder and arm was very extensive. A slide smear showed a staphylococcus infection of the wound. Blood cultures showed staphylococci in large quantities. The patient weighed about 130 pounds (59 kg.), and he was given, intravenously, one injection of 10 c.c. of a 1 per cent. solution of mercurochrome (a dose of only 1.7 mg. per kilogram). Following this he had a chill; the temperature, which was previously 104 F., went up to over 105, but in three hours fell to 102, and on the next day was 100, when he received another 10 c.c. of 1 per cent. solution intravenously. On the following day the temperature was normal. Two days later, the patient received a third dose (10 c.c. of a 1 per cent. solution), and on the following day blood cultures were taken which proved to be negative, and the patient had an uninterrupted recovery.

and a definite diagnosis of retroperitoneal abscess was made. The patient's temperature at 8 o'clock was 103.5. Examination of the urine showed an infection of colon bacilli. Ordinarily the patient would have been taken to the operating room for immediate incision and drainage of the abscess, but we decided to try an intravenous injection of mercurochrome, and 27 c.c. of a 1 per cent. solution, 5.4 mg. per kilogram, was given at 11 a. m. At noon, the temperature was 106, and the patient had a severe chill, but by midnight it had dropped to 99.6, and after that remained practically normal. On the following day the patient was free from pain, the muscle spasm had largely disappeared, and he went on to a rapid recovery without operation. Dec. 15, 1923 (final report), the patient was quite well.

The next case is somewhat similar:

CASE 4.—*Carcinoma of the bladder involving left ureter. Extensive excision with cautery. Two months later pyonephrosis on the left side, which disappeared after intravenous treatment.*

R. M., a man, aged 63, was admitted, June 28, 1923, the cystoscopic diagnosis being carcinoma of the bladder involv-

TABLE 1.—*Strength in Which Mercurochrome Appeared in Stools, Urine and Vomitus in Case 3 After Intravenous Injection.*

Hour After Injection	Stools			Urine			Vomitus			
	Number	Character	Concentration of Mercurochrome	Amount, C.c.	Concentration of Mercurochrome	Microscopic	Number	Character	Concentration of Mercurochrome	Comment
First.....	0	80	1:50,000	Smears negative; culture positive	1	Brown, with food particles	0	Became nauseated, 20 min. after injection
Second.....	1	Brown, soft	0	45	1:25,000	No organisms; few pus cells	2	Yellow	1:100,000	Sweating profusely; severe chill; temp., 106
Third.....	0	8	1:10,000	No casts.....	2	Fluid, yellow	1:100,000	Chill ended; temp., 103; pulse good; abdominal pain
Fourth.....	1	Fluid, yellow	1:10,000	10	1:10,000	0	Much more comfortable; sleeping; temp., 104
Fifth.....	0	40	1:10,000	No organisms; no casts	0	Temp., 106; complains of abdominal pain
Sixth.....	1	Fluid, yellow	1:25,000	0	Temp., 104; quite uncomfortable
Seventh.....	0	200	1:50,000	0	Taking fluids well; temp., 103; better
Eighth.....	1	Fluid, yellow	1:50,000	125	1:75,000	0	Temp., 100.8; much better
Ninth to twelfth	0	760	1:75,000	Cultures positive	9	Complains of abdominal pain; temp., normal
Thirteenth to eighteenth	4	Fluid, yellow tinge	1:100,000	720	1:100,000	No casts; albumin negative; smears negative	0	Abdominal pain much less severe; muscle spasm disappearing
Eighteenth to twenty-fourth	2	Mucous, yellow tinge	1:100,000	400	1:100,000	No casts; smears negative for organism	0	Temperature has remained 100 or below; much better
Second day....	1	Soft	0	1,000	Trace	Smears negative; culture negative	0	Temp., 99; condition improving rapidly
Third day....	2	Soft	0	1,200	Trace	Smears negative; culture negative	0	Temp., 98; patient feels almost normal; pain, tenderness and muscle spasm gone
Fourth day....	1	Soft	0	820	0	Smears negative; culture negative	0	Temperature has remained normal; patient feels well; up in chair

The cellulitis disappeared; the wounds healed completely, and the patient was discharged well.

The next case is not one of septicemia, but is equally interesting, in that an intravenous injection of mercurochrome resulted in the rapid disappearance of an extensive retroperitoneal infection (perinephric abscess) without operation.

CASE 3.—*Retroperitoneal abscess following bladder instrumentation. Colon bacillus infection. Intravenous injection of mercurochrome. Rapid disappearance of abscess.*

J. H. D., a youth, aged 17, admitted, June 21, 1923, had a hypospadias, for which a plastic operation was done to close the defect. The convalescence was uneventful until July 14, the twenty-third day, when, following the passage of sounds, the patient had a chill and fever which reached 101.5 F., as shown in Chart 1. On the following day, the patient was very ill, and the temperature reached 104. He complained of pain in the left side, extending up the small of his back, and on examination there was muscle spasm and tenderness on pressure. A diagnosis of retroperitoneal infection following instrumental laceration of the urethra or bladder was made. On the next day the muscle spasm and mass had increased,

ing the right ureter. July 9, a suprapubic excision was made, and extensive tumors were destroyed with the electric cautery. Radium was implanted and a small prostatic bar was destroyed. The tumor surrounded the left ureter, but, owing to the extent of the involvement, transplantation of the ureter was not undertaken. The patient did well until September 5, when he began to have intermittent fever with chills, and rapidly declined in strength. At the same time he developed a mass, tenderness, and slight muscle spasm in the region of the left kidney. He continued to have pyrexia and rapidly grew worse, until it seemed evident that a fatal ending would soon ensue.

Microscopic examination of the urine showed bacilli, streptococci and staphylococci. On the presumption that the patient had a left pyonephrosis, and as he seemed too ill for operation on the kidney, it was decided to treat him with intravenous antiseptics. September 23, he was given mercurochrome, 5 mg. per kilogram (28 c.c. of a 1 per cent. solution). Within two hours, the strength in the urine was 1:5,000, and during the third and fourth hours, 1:4,000. As late as the eighth hour, it was in a strength of 1:8,000 in the urine, which strength is of very distinct germicidal value. This injection had a most pronounced effect on the bacilli in

the urine. Within three hours, they had completely disappeared from the urine, and were no longer found during four days in which examinations were made. The gram-positive cocci were not reduced greatly in number, but the patient improved greatly, and his temperature fell to normal, and remained so for about two weeks. As the urine still contained large numbers of staphylococci and streptococci, he was then given 600 mg. of neo-arsphenamin intravenously, with very slight reaction. As a result of this injection, the staphylococci and streptococci present were both reduced slightly; but, as the patient soon began to have a temperature of from 99.5 to 100

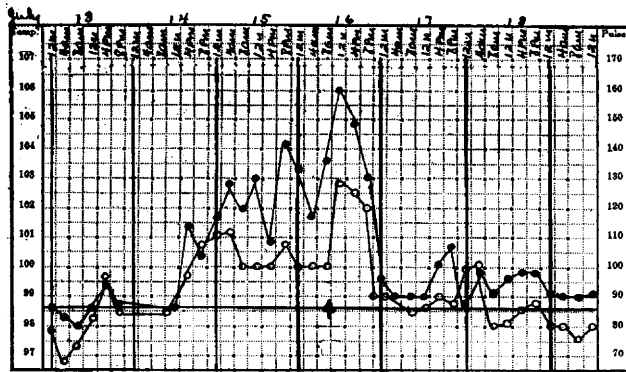


Chart 1.—Temperature (solid dots) and pulse (outline dots) in Case 3. Arrow indicates injection of mercurochrome.

daily, he was given 28 c.c. of a 1 per cent. solution of gentian violet (5 mg. per kilogram), October 11. This was followed by no reaction, and, within an hour, the gentian violet appeared in a strength of 1:100,000 in the urine, and remained at that strength until the fourth hour. The staphylococci did not disappear completely. The patient, however, was much better after the treatment, the fever disappeared, and from that time on he continued to improve steadily. The pain and tenderness in the region of the kidney disappeared, and he gradually regained his strength and weight, so that within two weeks he was able to be up in a chair. His condition was completely transformed, and, I believe, his life was saved. Dec. 25, 1923 (final report), the patient wrote that he was well and at work.

The following cases are cited to show the sterilizing effect of intravenous mercurochrome on local processes:

CASE 5.—*Bilateral chronic pyelitis due to Bacillus lactis-aerogenes. Treated by intravenous injection of mercurochrome with complete cure.*

A woman, admitted, Jan. 2, 1923, complained of pain in the left side of six months' duration, and of frequency of urination. The cystoscope showed the bladder to be normal. Ureteral catheterization showed pus and bacilli from the right kidney. A thorium pyelogram was taken of the left kidney and was negative. During the following week the patient was treated by pelvic lavage three times. Cultures were obtained from the right kidney, and were found to be *Bacillus lactis-aerogenes*. Cultures from the left kidney were at first sterile, but later showed bacilli. As the pelvic lavage was unsuccessful in clearing up the renal infection (both 1 per cent. sodium dihydroximercuri-dihydroxibenzophenone sulphonate (meroxyl) and 1 per cent. silver nitrate had been used), January 12, she was given an intravenous injection of 1 per cent. mercurochrome (5 mg. per kilogram). Marked nausea appeared thirty minutes after injection, and half an hour later there was vomiting and a large stool. In six hours the nausea had subsided and the patient was more comfortable. The temperature remained normal. On the following day the urine was found to contain numerous bacilli (probably dead), but the cultures were sterile. Casts were present for a few days, but on discharge from the hospital, January 26, the urine was sterile. There was only a trace of albumin, and only an occasional cast, and the pain and discomfort had completely disappeared. Subsequent cultural examination showed the urine to be sterile.

The next case is similar.

CASE 6.—*Chronic cystitis following prostatectomy. Colon bacillus and Staphylococcus albus infection sterilized by intravenous injection of mercurochrome.*

J. M. B., a man, aged 60, was readmitted, Oct. 13, 1923, complaining of frequency of urination. He had been subjected to a perineal prostatectomy one year previously, and a good result was obtained, with the exception of a vesical infection. Examination was negative except for cloudy urine with pus and bacilli present in large numbers. The patient was treated by intravesical irrigations with benefit, but the urine was still heavily infected with colon bacilli and a small number of cocci. October 12, he was given 20 c.c. of 1 per cent. solution of mercurochrome intravenously (about 3 mg. per kilogram). He had no reaction; no rise in temperature, no vomitus, and no stools. Within one hour the urine showed colorimetrically a content of 1:20,000 mercurochrome. After the second hour, cultures and slide smears were negative, and remained negative for bacteria until the patient was discharged from the hospital, two days later. Cultures obtained ten days later showed that the urine was still sterile.

CASE 7.—*Pyelitis due to colon bacillus. A child, very septic, apparently saved by mercurochrome intravenously.*

M. L., a girl, aged 4 years, weighing 26 pounds (11 kg.), was admitted to the Harriet Lane Home, Nov. 2, 1923, complaining of pain in the right side, of two days' duration. The patient was very sick; the temperature was 102.5, and the abdomen was rigid, with marked tenderness over both kidney regions. The urine was cloudy and contained pus and *B. coli* in large numbers. Leukocytosis was 19,950. A phenolsulphonaphthalein test yielded 55 per cent. in two hours. Blood culture was negative. Cultures from the urine showed *B. coli*. During the first two days the temperature reached 105, and on the third day the patient was very ill, and it was decided to administer an intravenous injection of mercurochrome. Accordingly, 100 mg. was given (8 mg. per kilogram). Following the injection, the temperature fell to 98. The next day the patient was much better, but continued to have a fever, and during the next five days received four intravenous injections of mercurochrome, 30 mg. each (2.5 mg. per kilogram). Under this treatment the temperature finally reached normal on the eighth day (Chart 2). She then developed a furuncle. The temperature rose to 102.5. Bacteria were still present in the urine.

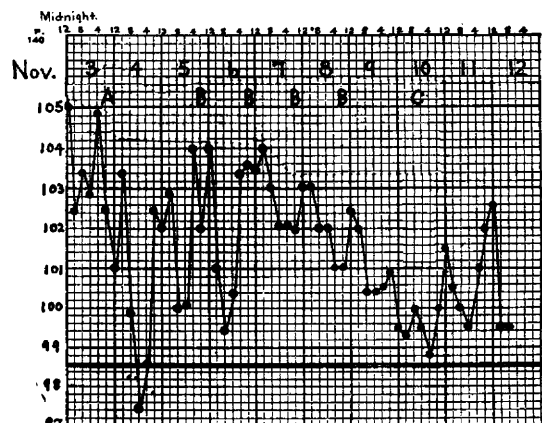


Chart 2.—Temperature in Case 7: A, 100 mg. of mercurochrome (8 mg. per kilogram); B, 30 mg. of mercurochrome (2.5 mg. per kilogram); C, furunculosis developed.

In addition to these seven cases, mercurochrome has been used intravenously in several cases of pyelitis and also other local infections. In some of the cases of pyelitis the urine was promptly sterilized. In others there was improvement, but bacteria still persisted in the urine. This was true also of a case of chronic prostatitis and cystitis with colon bacillus infection in which, after the injection of 6.8 mg. per kilogram, the organisms still persisted. In other cases, however, the sterilization of the urine was very prompt and perma-

ment after a single injection of mercurochrome in doses varying from 3 to 5 mg. per kilogram.

It is evident, therefore, that the drug is not efficacious in all cases, and it is probable that colon bacilli differ from one another in their resistance to mercurochrome just as they differ markedly in other respects. At the same time, these and other laboratory and clinical experiments show conclusively that often the intravenous use of mercurochrome may have a very prompt and effective sterilizing action.

USE OF GENTIAN VIOLET

In a recent article, Churchman,⁵ who in 1910, at this clinic, began his studies on gentian violet, which he has shown to be a remarkable germicide for gram-positive staphylococci, writes:

Tri-phenyl-methane dyes may be injected into the circulation of rabbits in pretty large doses without harm to the animals, and the blood of the injected animal possesses the

TABLE 2.—Antiseptic Action of Urine After One Intravenous Dose of Gentian Violet, 10 Mg. per Kilogram *

	Staphylococcus aureus per Cubic Centimeter				
	One Minute After Inoculation	One Hour After Inoculation	Two Hours After Inoculation	Twenty-Four Hours After Inoculation	Uninoculated Control
Urine obtained by catheterization 1 hour after injection.....	3,300,000	1,100,000	430,000	0	0
Urine obtained by catheterization 3 hours after injection.....	1,040,000	680,000	410,000	0	0
Urine obtained by catheterization 5 hours after injection.....	2,700,000	770,000	1,300,000	0
- B. coli					
Urine obtained by catheterization 5 minutes before injection (control)...	1,600,000	11,000,000	11,000,000	83,000,000	0
Urine obtained by catheterization 1 hour after injection.....	5,600,000	5,500,000	3,810,000	7,700,000	0
Urine obtained by catheterization 3 hours after injection.....	1,500,000	1,800,000	3,600,000	0

* Specimens obtained by catheterization, before injection and one, three and five hours after injection, and inoculated with *Staphylococcus aureus* or *B. coli*.

selective bacteriostatic property of the dye itself. But only for a short time. At the end of one and three-fourths hours it has entirely disappeared. This power which the blood possesses cannot be interpreted as an activation of the serum, but is due solely to the presence in the blood of the unchanged dye. When the dye is changed, as it is, in a relatively short time, the power disappears. It seems probable, since all dyes are rather unstable, that a similar change takes place in other dyes. I have never been able to kill organisms circulating in the blood by intravascular injection of gentian violet. There is some evidence in the literature that it may at some time prove possible to produce a sterilisans magna in this way; but certainly at the present time there is nothing to suggest that it is now possible to do for bacteria what quinin does for malaria.

We have studied the toxicity of gentian violet by intravenous administration of the drug to normal rabbits.⁶ An injection of 20 mg. per kilogram killed in five hours. However, single doses of 5 mg. per kilo-

gram (three rabbits), 7.5 mg. (two rabbits) and 10 mg. (four rabbits) have been well tolerated in every case. Repeated injections, given three times a week, have shown that of three rabbits given 5 mg. per kilogram, two died after the seventh injection, one tolerating seven injections well. Two rabbits died after four doses of 7.5 mg. per kilogram. Of four rabbits given 10 mg. per kilogram, one died after the fifth dose, one after the fourth, and two after the second, an average of about three doses. Further experiments with repeated injections of smaller doses are now in progress, in connection with pathologic studies. The series here reported, however, indicates that single doses of 5, 7.5 and 10 mg. per kilogram have so far been without toxic effects on rabbits, while repeated doses of these amounts have been sufficiently toxic to indicate that when series of injections are contemplated, smaller doses should be used, or, possibly, the intervals between injections lengthened.

The fact that urine may become bactericidal for staphylococci after the intravenous injection of gentian violet is shown by the following experiment:

The animal was catheterized with aseptic precautions, five minutes before injection, and one, three and five hours after injection. Two cubic centimeters of each specimen so obtained was placed in a sterile test tube and inoculated with one standard loopful of the test organisms. One minute after inoculation, 0.1 c.c. of this urine-organism mixture was removed, diluted and plated to determine the number of bacteria present. Similar tests were made by dilution and plating one, two and twenty-four hours after inoculation. In this way it was possible to estimate the increase or decrease in the number of bacteria, and so to determine the antiseptic or germicidal action of the urine. The marked increase in the number of bacteria in the urine taken before drug administration indicates that the urine was not normally antiseptic. The findings are expressed in terms of number of bacteria per cubic centimeter in Table 2.

The urine after administration of gentian violet intravenously became markedly antiseptic for *Staphylococcus aureus* and moderately so for *B. coli*. The drug showed bacteriostatic actions on *B. coli*, but was not bactericidal. In the specimens taken one and three hours after injection, the urine was bactericidal for *Staphylococcus aureus*, killing all the organisms during a twenty-four-hour exposure period.

Gentian violet was first employed as an intravenous germicide, July 12, 1923:

CASE 8.—*Ureteral calculus; Staphylococcus aureus urinary infection; intravenous injection of gentian violet; sterilization.*

J. D. G., a man, aged 47, first came to Brady Institute, June 29, 1923, complaining of attacks of pain in the left side. One year before he had an attack of pain in the left flank, associated with slight frequency of urination, and similar attacks at irregular intervals subsequently. At times the pain radiated into the testis. Examination of the urine after these attacks showed red blood cells. The attacks became more frequent and severe during the last few months.

Physical examination showed tenderness over the region of the left ureter. The urine was uninfected, but contained a trace of albumin. There were no red blood corpuscles. Roentgen-ray examination showed a shadow in the lower left ureter.

On cystoscopic examination, the bladder was normal. A wax-tip catheter met an obstruction 1 inch from the left ureteral orifice, and showed a scratch on withdrawal. Procaïn and oil were injected through the catheter.

The patient remained in the ward sixteen days, during which time he received two other injections of oil and procaïn without any change in the position of the stone. Six days following the first instrumentation, gram-positive cocci were found in the urine (*Staphylococcus aureus*). July 12, he received 50 c.c. of 1 per cent. gentian violet (7 mg. per kilogram of body weight). Except for a slight uneasiness in the abdomen, the

5. Churchman, J. W.: The Selective Bacteriostatic Action of Gentian Violet and Other Dyes, *J. Urol.*, January, 1924.

6. Coleman and Bell's gentian violet improved has been used throughout, experimentally and clinically.

patient had no reaction. Pulse, temperature and respiration remained normal. There was no nausea, vomiting or diarrhea. There was, however, quite a remarkable change in the color of the skin. It immediately became quite blue, giving the appearance of extreme cyanosis. This gradually subsided so that six hours later he appeared quite normal. He stated that all objects appeared purple immediately following the injection. Urine voided one hour after the injection had a quite marked violet tinge. Colorimetric tests showed gentian violet present in this specimen in a dilution of 1:50,000. The second hourly specimen contained the drug in a dilution of 1:100,000. There was a faint trace in all specimens for twenty-four hours. Cultures taken from each specimen contained cocci. A smear of a centrifugalized fresh specimen forty-eight hours after injection showed no organisms. Cultures taken at this time, however, showed an occasional coccus.

Three days following the gentian violet treatment, ureterotomy was performed and two small spiculated calculi were removed from the lower ureter. Cultures, September 24, showed no growth, indicating a complete clearing up of the infection.

The second case in which gentian violet was employed intravenously was a case of staphylococcus septicemia in the Harriet Lane Home, service of Dr. Howland. The report is furnished by Dr. Casparis, who gave the injections.

CASE 9.—*Infant with staphylococcus septicemia and multiple abscesses; gentian violet intravenously; sterilization of blood and cure of abscesses.*

Gentian violet was injected intravenously into an infant, aged 15 months, suffering from staphylococcus septicemia. This patient had been admitted to the wards three weeks previously suffering from severe bacillary dysentery and otitis media, and had later developed multiple large staphylococcus abscesses and staphylococcus septicemia. His condition had gradually grown worse; his temperature, which had ranged from 101 to 103, had finally reached 106, and he apparently was moribund. *Staphylococcus aureus* had been demonstrated in two cultures made during the three days preceding the first injection (Aug. 29, 1923). There were about 10 colonies per cubic centimeter of blood. Three injections of a 0.25 per cent. aqueous solution of gentian violet were given at twenty-four hour intervals. The first dose was 5 mg. per kilogram of body weight. The calculated resulting concentration of the dye in the body fluid was 1:140,000, on the assumption that the fluid content of the body is 70 per cent. of the body weight.

The white blood cell count, which was 22,000 at the time of injection, was reduced to 10,000 twelve hours later, but returned almost to the original count during the next twelve hours. Because of the possibility that the reduction in the white blood cell count was due to the effect of the dye in that concentration, the amount was reduced, and the second and third doses consisted of 4 mg. per kilogram of body weight. Blood cultures made immediately preceding the second and third injections were sterile. After the third injection the patient's appearance had improved, his fever was reduced, and the white blood count had decreased. We therefore discontinued the administration of gentian violet.

The child, whose condition was desperate at the time the injection of gentian violet was begun, gradually improved. He gained weight, the abscesses healed, and he was discharged from the hospital two months later, entirely well.

Another very severe case in which the patient was saved by gentian violet injections is from the surgical department, service of Dr. Finney, the report of which has been furnished by Dr. Rienhoff, resident surgeon.

CASE 10.—*Staphylococcus septicemia with multiple osteomyelitis. A boy, almost moribund. Gentian violet, 5 mg. per kilogram, intravenously. Blood sterilized.*

R. M., a boy, aged 6 years, admitted, Sept. 18, 1923, had multiple osteomyelitis and general septicemia. The temperature on admission was 102, and during the next five days it varied between 101 and 106. During this time the child

became progressively worse and practically moribund, with a temperature of 106. Acute osteomyelitis of the tibia, fibula, radius, ulna and humerus was present, and blood cultures showed *Staphylococcus aureus*. Multiple incisions were made for the osteomyelitis, and the cultures showed here also *Staphylococcus aureus* infection. At 8 p. m., September 23, the patient's temperature was 106.3, and, as a last resort, he was given gentian violet intravenously, 5 mg. per kilogram. The temperature began to fall at once, and reached 101 the next morning. The patient became conscious and improved steadily. Blood cultures taken two and three days later showed that blood was sterile. The patient continued to improve clinically, and, at the end of twenty-four hours, the temperature was 99, and he was apparently cured of the septicemia. On the forty-fourth day the left knee joint became inflamed, with a recurrence of the septicemia, and he was given another intravenous injection of gentian violet, 5 mg. per kilogram, November 15. Cultures from the blood three days later were sterile, but the fever persisted. The patient was given another intravenous injection of gentian violet, 5 mg. per kilogram, several days later. The osteomyelitic processes have not been completely cured, the urine is now infected and the patient has fever, but cultures from the blood show that it is still sterile (November 27), and the condition of the patient is steadily improving. Feb. 18, 1924 (final note), the sequestrum had been removed, and the boy was nearly ready to leave the hospital.

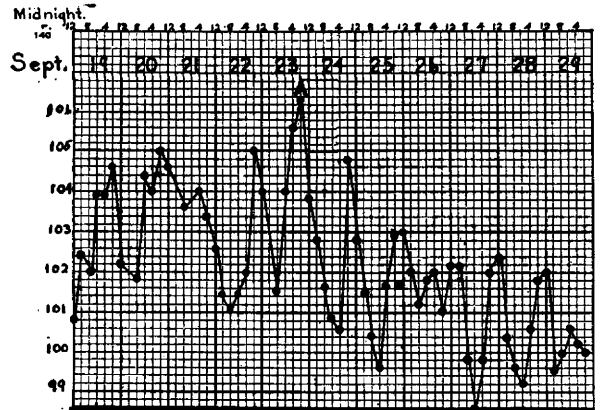


Chart 3.—Temperature in Case 10: A, gentian violet, 5 mg. per kilogram.

This is an interesting case as showing how general septicemia may come on from localized processes after being completely sterilized by an intravenous treatment of gentian violet. It would seem to indicate that, in addition to intravenous therapy, attention to the local processes is indicated in order completely to clear up chronic foci of infection. It is possible that multiple repeated intravenous injections would be advisable in such cases, but they would have to be given with care, as we do not as yet know the limit of safety for repeated injections.

CASE 11.—*Diabetes mellitus; staphylococcus septicemia; intravenous injection of gentian violet.*

F. S., a woman, aged 42, whose weight was 150 pounds (68 kg.), admitted, Aug. 25, 1923, complained of excessive hunger and thirst, and an abscess of the left palm. She had been sick for many years with various diseases. Six years before, she developed diabetes mellitus, and this was followed by multiple abscesses. Three days before admission, the patient developed an abscess on the palm of the left hand, which was draining on admission. Physical examination showed obesity, vascular changes in the retina with blurring of disks, pyorrhea, emphysema of the lungs, an enlarged heart with a systolic murmur, hypertension and arteriosclerosis. The knee kick and ankle jerk were absent; an abscess in the left hand and in each axilla were all draining pus. The Wassermann test was positive. The urine at this

time was negative for sugar. The patient was placed on insulin treatment, and did well until October 27, when she had a chill, followed by a rise in temperature to 105. Blood cultures were immediately taken, and showed a pure culture of *Staphylococcus aureus*, 40 colonies per cubic centimeter of blood. On the following day the cultures showed 140 colonies per cubic centimeter. The patient was desperately sick, the temperature varying from 102 to 104. October 29, she was given an intravenous injection of gentian violet, 5 mg. per kilogram. The culture taken before injection showed a great drop in the number of organisms. On the following day only one colony of *Staphylococcus aureus* was found per cubic centimeter of blood, and on November 4, blood cultures were sterile. By referring to Chart 4, it will be seen that the temperature by this time had reached normal. The patient was discharged, November 18, in excellent condition.

Because the blood culture taken before injection showed a great fall in the bacterial count, it is impossible to demonstrate clearly the action of gentian violet in this case, but it is probable that it at least aided the sterilization of the blood and the rapid recovery of the patient without spread of the infection.

Case 12 shows a selective action of gentian violet against the staphylococcus.

CASE 12.—Chronic cystitis, posterior urethritis, and prostatitis, due to staphylococcus, which was removed by gentian violet intravenously.

U. H. H., a man, aged 53, admitted, Nov. 10, 1923, complained of frequency of urination of one year's duration. Examination showed a chronic prostatitis, vesiculitis and cystitis. The urine contained pus and cocci in large numbers. Cultures showed *Staphylococcus aureus* and also a streptococcus. The patient was given an intravenous injection of gentian violet, 40 c.c. of a 1 per cent. solution. At the end of an hour, gentian violet was present in the urine in a strength of 1:200,000, and cultures from the urine remained sterile, beginning with the second hour. A culture taken on the third day again showed staphylococci absent, but a growth of streptococci still persisted. The patient had no reaction as a result of the injection; he did not vomit, and he had no diarrhea. He left the hospital improved.

This case is interesting as showing that the gentian violet is much more effective against staphylococci than streptococci, thus confirming laboratory experiments, which show that gentian violet in vitro prevents the growth of staphylococci in broth in a dilution of 1:1,000,000 or more, and streptococci in a dilution of 1:200,000.

SUMMARY

The cases comprise seven which were treated by mercurochrome, and five by gentian violet. The mercurochrome cases include two cases of septicemia—both desperate cases in which cure was effected and the blood sterilized by intravenous injection of mercurochrome. The results were almost miraculous, the patient being verily snatched from the jaws of death (Cases 1 and 2).

In Case 3, an ascending retroperitoneal infection, the disappearance of the inflammatory mass was just as startling.

In Cases 4 and 7, pyonephritis, the patients' lives were undoubtedly saved, and in Cases 5 and 6, pronounced *B. coli* urinary infections of the kidney and bladder disappeared almost immediately after a single injection of mercurochrome.

These cases are sufficiently varied to show a wide field of usefulness for mercurochrome-220 soluble as an intravenous germicide; but just what the limitations of its use may be will have to be determined by a much more extensive series of trials. In most of these cases, the organism has been one of the colon group, but one

of those reported here was a staphylococcus septicemia with extensive infectious processes in the chest, back and arm. Other cases, in which the drug was administered by others, and of which we have not complete notes, show that mercurochrome may be efficacious in streptococcus septicemias as well as in those due to the staphylococcus and colon bacillus. Feb. 18, 1924, since first presenting these cases in October, 1923, several septicemias have been treated, two *S. hemolyticus* and two *S. viridans*, without success. On the other hand, three cases of staphylococcus septicemia have been cured by gentian violet injections (reports from Dr. George Heuer, Cincinnati, Dr. F. M. Hanes, Winston-Salem, N. C., and Dr. John T. Geraghty). Dr. E. B. Piper, Philadelphia, writes that he has cured three staphylococcus and several streptococcus septicemias with mercurochrome.

In one case, a child, a dose of 8 mg. per kilogram of body weight was used once, and in one adult we injected 6.8 mg. per kilogram; but the patient had very severe nausea, vomiting and diarrhea, with a transitory albuminuria. Other patients who received 5 mg. per kilogram had pronounced gastro-intestinal symptoms, but all were transitory and after a few days the patients were normal. In urinary infections, the smaller dose may be justified and perhaps just as efficacious; but the desperate nature of septicemia demands drastic treatment, and 5 mg. per kilogram should be employed. That the drug is not always successful in sterilizing the urine has been pointed out.

The five cases treated by gentian violet comprise just as desperate cases as some of those treated by mercurochrome, and gave just as brilliant results. In all of these cases the infecting agent was a staphylococcus, and in our experience gentian violet has had an apparently selective action against gram-positive staphylococci. Cases in which it did not affect the streptococcus or the colon bacillus are cited, but our series of cases is still much too small to lay down positive dicta as to the selective action of these drugs for the various pathogenic bacteria of local and general infections. In the case of gentian violet, the intravenous injection of 5 mg. per kilogram is immediately followed by a most alarming cyanosis, which is simply due to the dye in the blood, which causes no harm and passes off in a few hours. Otherwise, practically no reaction results, and we have administered 8 mg. per kilogram of body weight in 0.5 per cent. solution without harm. The pulse may get quite slow (60) and the blood pressure drops. In very feeble patients, cardiac stimulants should be administered. In very weak patients, the injection may best be given in two or three treatments (intravenous) one hour apart, in order to give large doses.

In these cases we have the first demonstration that gentian violet may be used intravenously to combat general septicemia or local infections, and with remarkable success in the case of gram-positive staphylococci. Coupled with the equally amazing results obtained by mercurochrome, these cases represent a splendid therapeutic achievement, and one is tempted to soar into realms of fancy and see a great variety of infectious processes treated and cured intravenously; but one must be restrained and cautious. Only by most careful study and painstaking selection and management of the cases can serious blunders be avoided, and it would not be safe as yet to risk not operating on certain fulminating infections that can now be cured by prompt surgery. That certain localized infections may now be safely subjected to the experimental use of intravenous

therapy is shown by some of these cases, and there can be no doubt that when blood cultures show a generalized septicemia, mercurochrome and gentian violet can now be offered with the hope of preventing an otherwise surely fatal ending.⁷

SURVEY OF THE NARCOTIC PROBLEM *

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In June, 1923, questionnaires were sent to all physicians and dentists in the state of New York. The one to the physicians asked:

Amount of morphin prescribed in 1922?

Amount of heroin prescribed in 1922?

Amount of cocain prescribed in 1922?

Number of narcotic addicts treated in 1922?

Do you believe that heroin is necessary in your practice?

Do you believe that cocain can be advantageously replaced by non-habit-forming synthetic drugs, such as procain or similar preparations?

The one to the dentists asked:

Amounts of cocain used in 1922?

Do you believe that cocain can be advantageously replaced by non-habit-forming synthetic drugs, such as procain or similar preparations?

The animating purposes in making these inquiries of physicians and dentists, as to the practical experience acquired in their professional use of habit-forming drugs, were:

1. To determine whether this is a medical issue or a police problem, or both.

2. To gain statistical knowledge as to the number of medical drug addicts treated in this state during a given period of time, from which reasonable approximations or conclusions may be drawn.

3. To ascertain the quantity of narcotics prescribed by the physicians and dentists in the state of New York. No attempt was made to ascertain the amount of narcotics consumed by the public and furnished to the market legitimately through druggists in the form of paregoric, proprietary medicine, etc., nor were hospitals taken into consideration. It was my opinion that addicts treated in hospitals had previously been under treatment in the private practice of physicians. Therefore, in order to avoid duplication, no hospital statistics were gathered.

4. To obtain general information as to the desirability and possibility of the practitioner's substituting non-habit-forming drugs, without lessened efficacy of his service to his patients.

5. To secure information as to the necessity of heroin in the practice of medicine. There was no intention to suggest any restrictions to the constitutional right of the physician to prescribe whatever he deemed necessary to his practice. In the light of the investigations here reported and which may hereafter be made, the profession itself should determine whether the physicians themselves should not unite in declaring heroin an outlawed drug.

6. To ascertain the quantity of cocain used by dentists and physicians; to determine the percentage of practitioners who, in part or wholly, employ synthetic

preparations having no habit-forming qualities, and to learn, from those competent to judge, the efficacy of these substitutes.

It was my intention to find out what narcotics are necessary and the extent of their use and, in general, to show through the census the general trend.

Far from attempting to minimize the work of the practitioner, my aim has been to gather information so that the various points of view of the physicians and dentists may be available for mitigating and eradicating evils in connection with the use of habit-forming drugs.

The responses to this appeal from the medical and dental profession have been most hearty, and again furnish exhaustive evidence that the professional man is an altruist in lending his aid in the solution of great public issues. It is to be hoped that the data secured will be helpful in solving some of the vexatious problems that obtrude. The following is a review of the returns received from the questionnaire:

IS DRUG ADDICTION A MEDICAL ISSUE OR A POLICE PROBLEM?

Some medical men have been of the opinion that all that pertains to this subject should be under the jurisdiction of the medical profession; that drug addiction is a sickness or a disease, and the addict should be regarded and treated as a sick man. On the other hand, most of those administering the criminal laws, supported by the great majority of social workers, contend that, because such a large percentage of criminals have acquired the narcotic habit, the issue has become one inseparably connected with the regulation of crime.

The returns show that there is a medical narcotic addict who requires narcotics because of physical ailments. This type is obviously one to be handled by physicians, and every barrier should be removed so as not to embarrass the physician in according relief to such sufferers.

The far greater number, however, are the criminal drug addicts whose addiction in its inception and in its continuance is due to vice, vicious environment and criminal associations. The consideration of this class, the figures prove, constitutes a distinct police problem. The so-called medical addict who will not consult the physician, but purchases his narcotics from street vendors and thus supports the illicit traffic in drugs, obviously places himself in the same class as the criminal addict. In about 10,000 arrests and hospital commitments for cure by the narcotic division of the police department during the last three years, it was frankly admitted by 98 per cent. and a fraction that their addiction was due to bad associations; that there was never any medical reason for their using narcotics. The remaining 2 per cent. gave various excuses for first using narcotics, principally some surgical operation or illness. At the time of their arrest there was in this minute percentage almost invariably no reason for their continuing to use narcotics, surely not for the use of heroin and cocain. They buy these on the street, knowing that no reputable physician will prescribe for them. The medical addict usually confines himself to morphin, but the menu of the criminal addict is heroin and cocain. Approximately 95 per cent. of those arrested by the police in New York City are heroin and cocain users. In other parts of the country, morphin is the chief narcotic.

Heroin addiction is, however, rapidly replacing morphin addiction throughout the United States, this spread being more noticeable from seaport cities.

7. Young, H. H.: Cure of a Retroperitoneal Abscess by Intravenous Injection of Mercurochrome. *Bull. Johns Hopkins Hosp.*, January, 1924; *Urinary Antiseptics*, *J. Urol.* 11: 19 (Jan.) 1924.
* Read before the Medical Society of the County of New York, Jan. 28, 1924.