rather as belonging to that group of infections which may be designated *general* and not readily distinguishable from the bacteria of wound infection. In a sense they apparently repeat in the genital tract analogous bacteria normally resident upon the skin, virtually harmless upon the unbroken surface with high potentiality for harm when a wound occurs.

The important point is that sexual excess has in cattle a concrete meaning. The data are as yet fragmentary but capable of unlimited extension by research. *(For discussion, see page 563.)*

THE TREATMENT OF PUERPERAL SEPSIS BY THE USE OF MERCUROCHROME INTRAVENOUSLY WITH A REPORT OF ANIMAL EXPERIMENTATION IN THE CHEMICAL DISINFECTION OF THE BLOOD*

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THE subject of puerperal sepsis and its treatment has been the cause of acrimonious discussion within the medical profession since the days of Hippocrates. Most of this discussion has been upon the etiology and the predisposing factors in the causation of this condition. Arnold Lea has a very clear cut and a delightful description of the historical side of this controversy. He speaks of "puerperal infection as the general term applied to all infected conditions which arise from the entrance of organisms into wounds of the generative tract in connection with labor or the puerperium," and further states that "all cases of fever during the puerperium, unless clearly attributable to some extraneous cause, should be considered as forms of wound infection." Polak in his monograph on "Pelvic Inflammation" states; "we know from clinical experience that the presence of decidua or a piece of placenta retained in the uterus will not cause endometritis unless infection is also present," and also that "puerperal fever is primarily due to infection of the obstetrical wound by microorganisms."

Mercatus, writing in 1570, was apparently the first observer to mention putridity of the lochia as an essential feature of the disease. In 1843 Oliver Wendell Holmes published his classical essay on the contagious nature of the condition.

*Read at the Forty-Seventh annual meeting of the American Gynecological Society, Washington, D. C., May 1-3, 1922

†(The author wishes to extend his thanks to Dr. Thomas McMillan of Philadelphia by whom the actual laboratory work was done, both in the original animal experimentation and the clinical controls.)

All students of this condition now agree there must be two things to cause puerperal sepsis. First, the presence of an obstetric wound and second, the presence of a pathogenic organism. Of necessity there must always be the obstetric wound and according to Polak's observation, 50 per cent of patients examined showed bacteria in the uterine cavity six or seven days after delivery. It would therefore appear that if these were the only two factors in the presence or absence of puerperal sepsis, its occurrence should be more frequent than it is at present. Fortunately however, the factor of the individual resistance is probably the greatest determining factor for or against the presence of local puerperal infection.

The term puerperal sepsis is, I believe, used very loosely. From the point of view of treatment alone it would seem necessary to make some distinction between puerperal sepsis, as a blood-stream infection, and as some local infection of the birth-canal. We may say in the old truism we were taught in logic, all cases of puerperal sepsis are puerperal infections but not all cases of puerperal infection are puerperal sepsis.

We are not considering here the absorption of the toxins from retained lochia. We all know that this frequently gives rise to all the symptoms and the graphic temperature chart of a true puerperal sepsis. It would be difficult to differentiate between a puerperal septicemia unproved by positive blood culture and a beginning localization where no localized symptoms have yet presented themselves. We have all seen those cases in which we have, not only a true septicemia but also the local condition as well. The most frequent of these, probably would be streptococcic peritonitis with an infection of the blood stream by the same organism.

As stated before, practically all cases of septicemia are due to infections implanted upon some obstetric injury to the maternal birth canal, but we must not lose sight of the fact that a woman in her early puerperium would be more likely to contract a blood stream infection from some extraneous cause, such as abscess of the teeth, etc., than she would at any other time, though this is rare.

It would seem therefore extremely difficult to differentiate between puerperal infections and puerperal sepsis but as a suggestion it would appeal to me that the latter term should only be used in those conditions, in which there is a definite proof of transmission of infection by the blood stream or lymphatics from the birth canal, and that we speak of every other infection depending upon the child-bearing act as a puerperal infection.

Treatment, in puerperal infection, might be divided into supportive, eliminative, local and blood stream. Under the supportive treatment would come stimulation and feeding. Naturally all cases would

be treated symptomatically. The replies to a questionnaire, sent out by Dr. Hirst, to some of the teaching hospitals, have shown considerable divergence of opinion along different lines of treatment. The question of alcoholic stimulation is fairly evenly divided. We believe in it strongly and use it in large amounts, also the administration of glucose by proctoclysis. We have used nuclein in the attempt to increase the leukocytes, and also autogenous antistreptococcic vaccine, the latter having very excellent results but unfortunately in the very serious cases, which terminate rapidly, we cannot wait for the preparation. In that type of case nothing seems to be of any value.

As to elimination, we keep the bowels open, give water by mouth when possible, otherwise by proctoclysis.

Under local treatment the much mooted subject of the intrauterine douche must be brought up. It is our practice in the University Maternity to irrigate with a return flow intrauterine douche tube those cases which show symptomatically the suspicion of some retention, or where there is a sudden stoppage of lochia, and in those cases where there is an occasionally foul discharge. This is not done with the idea that it is a specific cure for a general infection. We do not believe that we can cure any cases of blood stream infections by this method, but that in this manner we establish good drainage and attempt to keep the endometrium as clean as possible. The force of the flow is not sufficient to do any damage by way of the tubes. We do not believe that we have ever seen any bad results from this practice and we are sure that we have seen many cases rapidly clear up, but it must be understood that it is never done except for a local condition. As to operative treatment, where localization has definitely occurred, I believe that it is generally agreed that, where possible, it should be drained from below, but where there is a definite cornual abscess, suppurative metritis, infection and suppuration of the upper portion of the broad ligaments, tubes and ovaries or localized suppurative peritonitis above Douglas' pouch, we open the abdomen and drain.

Since 1900 there have been many different methods of intravenous treatment for puerperal septicemia, bichloride of mercury, magnesium sulphate, protargol, colloidal silver, eusol, phylacogen, arsenobenzol, formic aldehyde, phenoiodine, ammoniosulphate of copper and others.

Most of these have been reported to be attended with some degree of success. Polak's frequently repeated small blood transfusions have given excellent results in some cases. Antistreptococcic serum has given brilliant results in some cases and others were entire failures. When we use it, we do so in doses of 100 c.c. intravenously. Colloidal

silver and arsenobenzol have given us no results whatever but I am informed that in other clinics they have cleared up cases brilliantly.

In the winter of 1920, I had the misfortune to have a patient develop puerperal sepsis. She was a multipara, delivered normally in the hospital without instruments, with, I believe but one vaginal examination before delivery. However, she was admitted to the hospital in labor the same day that a patient died of streptococcic septicemia. The cause of the death in this case was known at the time, and the most careful precautions were taken, and yet this patient was infected and virulently so. The case from the beginning to the end made a peculiarly deep impression upon me because I felt that, had her resistance been better, in spite of the unfortunate fact of the death in the ward, everything would have gone well, but this girl's resistance was below par, both physically and mentally. She had been deserted by her husband some months previously and her mental attitude, when I first saw her was one of entire indifference to her recovery. This factor may be fanciful, but I believe it to be of importance. During the time in which this case was under my observation and care, a great deal of my time was spent in consideration of methods and treatment, and as many before me have no doubt thought, if we could find a germicide which, injected in the blood stream would kill the microorganisms and at the same time not kill the patient, we would be well on the way to the cure of the condition. Young, White and Schwartz in their paper from the Johns Hopkins Urological Clinic on the local use of mercurochrome in infections of the bladder had stated that the toxicity of this preparation had been tested by the injection into the veins of a rabbit. It had been found that in the ratio of 5 mg. per kilo of body weight the animal showed no ill effects, but that in the dosage of 10 mg. per kilo of body weight the animal was killed, and that a dog was able to take 10 mg. without any apparent ill effect. This showed us that we had very little leeway as to dosage.

After a consideration of this report, the following experiments were then carried out by Dr. Thomas McMillan, of Philadelphia, with the aid and valuable suggestions of Dr. Herbert Fox, director of the William Pepper Laboratory. I may say that this work was not entirely unattended by danger. Dr. McMillan was confined to the hospital with a virulent hemolytic streptococcic infection of the hand. His successor in the work, Dr. Hoehn, the pathologic resident at that time, soon after was sent to the Municipal Hospital with scarlet fever. The latter part of the work was done by Dr. McMillan after his recovery.

GERMICIDAL EFFECTS OF MERCUROCHROME "IN VITRO"

In their original work on mercurochrome, Young, White and Schwartz showed that this drug displayed a marked germicidal action on *S. aureus* and *B. coli* when these organisms were suspended in sterile urine.

They found that *S. aureus* was killed by a 1:5000 dilution of this agent in 5 minutes, while *B. coli* was killed in 15 minutes.

We attempted similar observations using defibrinated blood as the medium of suspension and a hemolytic streptococcus as the organism. The organism used was from a virulent case of puerperal septicemia. Blood agar slants were prepared from a 24-hour blood culture plate. These were incubated 24 hours.

Using the safe dose for the rabbit, 5 milligrams per kilo of body weight found by these workers, it was thought that in the human body this would represent a proportion of about 1:13,000 of the drug, therefore the dilutions used by us were 1:8000 and 1:16,000. In a 1:8000 dilution of mercurochrome in defibrinated blood, hemolytic streptococci were killed in 40 minutes. In a 1:16,000 dilution, plates prepared at the end of one hour showed two colonies. Those prepared after this showed no growth.

THE EFFECT OF MERCUROCHROME WHEN INTRODUCED INTO THE BLOOD
STREAM OF NORMAL RABBITS

We were guided in the dosage used by the workers referred to above. In accordance with their findings an apparently healthy rabbit weighing 2.4 kilos was given mercurochrome intravenously in the proportion of 5 milligrams per kilo of body weight. The stock solution used was a 1 per cent watery solution. Before the introduction of this drug a urinalysis showed an apparently normal urine. A blood count was done before the introduction of the drug and this gave an entirely normal figure. At intervals after the initial and subsequent doses of this drug blood counts were repeated. Practically no change was noted in the red blood count, and the white blood count was found to vary in the different examinations not more than 3,000 cells. The differential count was not materially changed. Following the initial dose of this drug, identical amounts were given directly into the vein at 24-hour intervals for three days. During this time there was no demonstrable hemolysis as judged by the macroscopic test, hemoglobin determinations, red blood count or urine examinations. After these three injections at 24-hour intervals no drug was given for a day. The injections of the drug were resumed, however, now being given in the proportion of 7 milligrams per kilo of body weight at intervals of 48 hours until three injections

were given. Therefore, in 14 days this animal was given 10.6 c.c. of a 1 per cent solution of mercurochrome intravenously, the last three doses in the proportion of 7 milligrams per kilo. During this time we were unable to demonstrate any urinary changes except a questionable trace of albumin on two occasions; casts were never found. We were unable to demonstrate mercury in the urine. The rabbit was then killed. At autopsy, there were no lesions found in any organ. The kidneys were particularly studied; neither grossly nor microscopically could any pathologic lesions be demonstrated. After an examination of the organs, the skin of the rabbit was removed, the body macerated and examined for mercury. The test was entirely negative.

THE EFFECT OF MERCUROCHROME ON ARTIFICIALLY INDUCED STREPTOCOCCIC INFECTIONS

A streptococcus recovered from the blood stream of a case of puerperal septicemia was used for these tests. Realizing that the streptococcus lost its virulence when kept for any length of time on artificial media, a blood agar slant was inoculated from a colony of a 24-hour blood culture plate. For the first rabbit used this slant was incubated 48 hours; 2 c.c. of a normal salt solution were then added and the bacterial growth emulsified. One c.c. of this bacterial emulsion was then injected into the ear vein of a rabbit. Blood cultures were taken at intervals from this rabbit. Plates taken 26 hours after inoculation showed the most abundant growth. In this rabbit, blood cultures remained positive until 48 hours after the introduction of the streptococcus; after 56 hours the blood cultures were consistently negative, and the rabbit recovered. Feeling that we had allowed the organisms to remain too long on artificial media, blood agar slants were again prepared from 24-hour blood culture plates of this rabbit and incubated for only 18 hours. Bacterial emulsions were then prepared. Simultaneously 1 c.c. of this bacterial suspension was then injected into the ear of two healthy female rabbits of approximately the same age and size. One rabbit was allowed to run its course untreated as a control and the other rabbit was treated with mercurochrome intravenously.

The untreated rabbit showed positive blood cultures and died within 36 hours. Cultures from this rabbit were then prepared. The heart, lungs and other organs of this rabbit yielded streptococci in great abundance.

The rabbit treated with mercurochrome, twenty-four hours after the introduction of the bacteria, was comatose, lying on its side, with its head markedly everted, and with the cornea of the left eye almost opaque and the sclera much injected. A blood cul-

ture at 24 hours was strongly positive. At this time mercurochrome in the proportion of 5 milligrams per kilo was given intravenously. Blood cultures at 26 hours and 29 hours were strongly positive. Twenty-nine hours after the injection of the bacteria, and five hours after the injection of the mercurochrome, the animal was distinctly better and was sitting erect and eating; the head was still held somewhat everted. Eleven hours after the first injection the head was practically straight and the animal was eating heartily. Twenty-two hours after the first dose of the drug the animal was worse again, lying on its side, breathing shallow and rapidly. The eye condition was very much worse; a panophthalmitis was present with the anterior chamber filled with free pus. Blood cultures taken at this time were positive, 26 hours later or 48 hours after the first injection of mercurochrome, blood cultures were still positive, and mercurochrome in the same strength was administered intravenously. Seven hours after this injection, the blood culture was faintly positive, 24 hours after this second injection the animal was distinctly better, and the blood culture was negative. Blood cultures were taken at frequent intervals after this but no positive cultures were obtained. The cornea of the left eye was very opaque. Feeling that the infection was still active here in spite of the negative blood culture, a third dose of the mercurochrome was given; blood cultures again were negative, and the animal clinically practically well. However, we were misled by the appearance of the eye into believing that pus was still present. It was decided to attempt an enucleation of the affected eye. The animal did not survive the anesthesia. At autopsy we were unable to recover streptococci from any organ, and to our great surprise it was found that although the interior of the eye was destroyed, no streptococci could be obtained. The lungs showed signs of a recent pneumonia but no streptococci could be recovered. We feel that mercurochrome in this instance, saved the life of a rabbit that was comatose with a pneumonia, an eye full of pus, and a blood stream infection, following the introduction into its circulation of a virulent streptococcus,—a strain that caused another rabbit of approximately the same size and weight, to die in 30 hours.

Following the death of the untreated control animal, a bacterial suspension was prepared from a twenty-four hour old blood culture plate of this rabbit.

Another rabbit was then given mercurochrome intravenously in the proportion of 5 milligrams per kilo. One minute after the introduction of this drug into the blood stream, 1.5 c.c. of the streptococcic emulsion was introduced into the circulation. Blood cultures were taken at frequent intervals. These were consistently negative. Ninety-six hours after this procedure, an additional 1.5 c.c. of the

streptococcic emulsion was given the same rabbit in order to see if the effects of mercurochrome persisted. Blood cultures were positive at twenty-two and forty-eight hours. Blood cultures were negative at ninety-six hours.

During the observation on the rabbit treated with mercurochrome, blood cultures becoming negative, our streptococcus was allowed to remain on artificial media too long. Therefore when the next rabbit was injected the culture proved entirely innocuous. In an attempt to increase the virulence of the strain this organism was passed successively through six mice intraperitoneally. The virulence of the organism for mice was greatly increased by this procedure. However, we were unable to gain back a permanent and persistent virulence for rabbits in this organism. Some eighteen rabbits in all were injected with various cultures of this organism but without its ever gaining a uniform virulence. All told, we used over thirty animals, but the results in all cases were not at all conclusive, and, owing to the difficulty of getting uniformity in the animals themselves, other results were not satisfactory.

To sum up, we felt that the experimental work showed that mercurochrome could be introduced into the blood stream of rabbits in certain strengths without any demonstrable harmful effects. We demonstrated also that mercurochrome in dilutions, considerably weaker than those we are able to introduce into the blood stream had distinct germicidal power. We were unable to consistently set up an active blood stream infection in all rabbits. However, we believe that in the case of one rabbit, at least, an animal that was comatose and with an eye full of pus,—this drug manifested spectacular power. Further we believe that in that particular rabbit the drug not only cleared up the blood stream infection but it actually attacked and showed germicidal power upon the local lesions.

Following our experimental work, we felt that we were justified in attempting the use of mercurochrome clinically. But in order to be on the safe side, we at first only tried it on cases that were actually moribund. The first case in which it was used was a woman admitted *in extremis*. Her temperature was 105° F., pulse approximately 160, respiration 40 to 50, she was unconscious and had all the signs of diffuse peritonitis. The drug in her case reacted, as in our later work, with chill, the dropping of her temperature and pulse for a short time and then she promptly died. We tried this again on one or two other cases of a similar nature with the same results. Although these patients died we could see no way in which the mercurochrome had hastened their end, in fact we thought we saw some slight improvement even in these desperately ill individuals.

We used this treatment on other cases, five of which are herewith submitted.

CASE 1.—H. B. Patient admitted to the hospital with a severe thrombophlebitis of the lower extremity. We were unable to obtain a positive blood culture. For days and weeks she ran a typical septic temperature. She was given anti-streptococcal serum with no benefit whatever. She gradually became worse and worse until it was thought she could not possibly live more than 48 hours. It was then determined to try mercurochrome intravenously. At this time her leg was almost gangrenous. She was given repeated doses of mercurochrome, of a smaller dosage than we now know can be given safely. The reactions were very marked and she was always clinically better after each dose. At the time that the first dose was given, a blood culture was taken and subsequently found to be strongly positive. Later it became negative under treatment. The patient eventually died of what appeared to be streptococcal pneumonia. At the time of her death, the local lesion in her leg had practically cleared.

CASE 2.—H. S. Patient with a positive blood culture of streptococcus viridans. She was given repeated doses of mercurochrome with rather strong reactions, the

Fig. 1.—Temperature chart from a case of puerperal sepsis, showing high and low daily temperature and recissions after administration of the mercurochrome.

patient always became clinically better. Inasmuch as the results in this type of infection have been uniformly bad, with all kinds of treatment, I did not anticipate any good results. After some weeks of treatment, she insisted upon going home and subsequently it was reported that she died.

CASE 3.—S. S. Puerperal septicemia with a hemolytic streptococcus in the blood. She was treated with mercurochrome with very slight reaction, subsequently she was treated with antistreptococcal serum with no apparent benefit. Eventually the condition localized as a cellulitic phlegmasia of the lower extremity which was opened and drained and the patient made a good recovery. Whether the mercurochrome in this case was of any value cannot be determined but the patient eventually showed a negative blood culture.

CASE 4.—Case of puerperal sepsis of long standing, admitted to the hospital after two months. She had had a thrombophlebitis of the lower extremity which appeared to have improved. Soon after admission she became suddenly worse, the temperature mounting rapidly. Her blood culture showed a hemolytic streptococcus

and she was given mercurochrome. This patient received the largest dose we had ever given up to that time. Her reaction and clinical improvement, as can be seen by the chart (Fig. 1) was very satisfactory. For 12 days her highest temperature at any time was 100.4° F. One dose of the drug was all that was given for a period of two weeks. One week after the first dose her blood culture was negative. Since that time her temperature has risen again, and she was given a second dose, April 27, to which she reacted in the usual manner. Naturally, I am unable to give the end result but she appears to be better.*

CASE 5.—Patient with a moderately severe case of pyelitis. She was not pregnant. She received two doses of mercurochrome three days apart. Her symptoms all disappeared but she still had pus in her urine. Her phthalein elimination was 30 per cent before her first dose and 35 per cent two days after her second dose.

In all cases there are a few points to be noted. The urine in all was typical of any severe infection. The mercurochrome did not change this in any way. The blood picture was in no way changed except that the leukocytes were somewhat increased in some instances. The phthalein test in one case was most satisfactory.

These cases are certainly not definitely conclusive that in mercurochrome we have found a specific cure for blood stream infections, but we feel that we may perhaps after more extensive observation find a way to increase the dosage, so that our subsequent results will be better. In a condition of this kind, in which there is some focus of infection, if we can kill the bacteria that are in the blood stream, the best we can hope for is that by so doing we can give the human organism a chance to cure itself.

The laboratory findings show that the dosage of the drug will of necessity be an important factor. Our original plan gave us a fairly good margin of safety. We gave that dose which was definitely shown to be nontoxic to the rabbit, that is, 5 milligrams per kilo of body weight. That would be about 25 c.c. of a 1 per cent solution of mercurochrome in distilled water for every 125 pounds of body weight. We definitely did not get as good results as we had hoped from this dosage. In case No. 4 as shown above, the dosage was somewhat higher, and based on her case, we feel safe that a nontoxic dose would be 25 c.c. of a 1 per cent solution per 100 pounds of body weight; in her case it was slightly larger. Naturally the body weight is an approximated figure.

The reaction that occurs is almost routinely the same. Within the first hour there may be vomiting; in less than two hours a definite diarrhea will commence. In the first six hours there will probably be a marked chill with a rise in temperature up to 105° F. Following this chill there will be a gradual decrease in temperature with a proportionate pulse rate decrease until the temperature reaches sub-normal, gradually rising to normal or slightly above where it should

*Subsequently, this case made a complete recovery and was discharged.

stay from 24 to 48 hours. The diarrhea will continue over a day or so and may require treatment.

Our technic is as follows: A solution of mercurochrome is prepared with sterile distilled water in 30 to 50 c.c. ampoules of a 1 per cent strength. It has been shown by other investigators, which our experience corroborates, that the drug loses its strength unless freshly prepared and for that reason we have it put up in ampoules, after we have determined upon its use. We never carry any solution on hand. It should never be used unless the solution is absolutely clear. The administration is done with a fine needle and a large syringe at a temperature as near 100° F. as possible and the injection made very slowly. Formerly at the end of twelve hours, the patient received a dose of magnesium sulphate. We no longer do this. Her reactions are treated symptomatically. We use external application of heat for the chill and a bismuth mixture as an intestinal sedative for the diarrhea, if it continues too long. A careful record of urinary output must be kept, as it will run below normal owing to fluid output by the bowel. Subsequent administration of the drug may be done. We make it a rule never to repeat as long as there is any sign of the dye in the urine or bowel movements. We have given as many as five doses. Salivation occasionally occurs.

For six months, we had extremely poor results in the few cases in which the drug was used. During that time we gave a dose of salts almost immediately after the injection of the drug. This method was employed in Case 3. It would appear that in so doing we had eliminated the drug before it had a chance and failed to get its germicidal effect.

The reaction that follows the intravenous injection of mercurochrome is analogous to that observed after the introduction of serum, bacteria or sterile milk by a similar route, and is probably explained in the same way. Some of the action of this drug may result from the immobilization or inhibition of the circulating germs, possibly also their direct destruction as in the test tube, aided by an increase of leucocyte activity which always accompanies postinjectional reactions. We have also reason to believe that mercurochrome may reduce the number of circulating organisms by combating them at the localization of the infection. The greatest value of this chemical is known to be in local infection.

CONCLUSIONS

1. There are certain cases of puerperal septicemia so fulminating and virulent that no treatment can possibly save them.
2. The use of antistreptococcic serum has appeared to be of great value in some cases. Frequently repeated small blood transfusions

are of value, as apparently are other methods of intravenous medication.

3. A solution of mercurochrome given intravenously in the proper dosage, appears, in some cases, to be of great value and to have no deleterious effects.

4. All cases of puerperal septicemia are so serious and so frequently fatal that heroic measures are justified.

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1936 SPRUCE STREET.

(For discussion, see page 565.)