# STREPTOMYCIN, AUREOMYCIN AND CHLOROMYCETIN: EXPERIMENTAL AND CLINICAL COMPARISON*

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Repeated reports have demonstrated the effectiveness of penicillin, streptomycin and the sulfonamides in peritonitis. In addition, preoperative use of these agents has been found to be of value in reducing the incidence of peritonitis in those surgical conditions in which, in the past, it has been relatively high.

Domagk[1] demonstrated the value of sulfonamides in the treatment of peritoneal infections in mice. Bower[2] and his associates tested the effects of prontosil on the mixed type of peritoneal infection commonly seen in human peritonitis, while Epps[3] and his associates compared the merits of sulfanilamide and sulfathiazole. Fauley *et al.*[4] studied the influence of penicillin in experimental peritonitis in dogs. Crile,[5] in a clinical study, reported the results of treatment with penicillin of peritonitis of appendiceal origin.

Murphy, Ravdin *et al.*[6] have studied the effects of streptomycin in experimental peritonitis in dogs, and, in addition, have shown that it passes into the peritoneal cavity, and frequently reaches a higher concentration than in the blood.

Kay and Lockwood,[7] in their experimental studies, expressed the thought that peritonitis is a systemic disease. This was based on their gross and microscopic findings at autopsy. They believed that changes in prothrombin time might be of prognostic value.

Pulaski,[8] in analyzing a series of clinical cases with peritonitis, stated that streptomycin, used alone, is especially effective in spreading and in localized types of peritonitis without a palpable mass. In a personal communication, he states that treatment of early spreading peritonitis with streptomycin and penicillin combined, seems to offer no significant advantage over streptomycin alone. He states, however, that in the management of localizing lesions, combined therapy seems superior.

Several additional antibiotics have been developed since the discovery of penicillin and streptomycin. Bacitracin, aureomycin and chloromycetin are representative of this new group. Bacitracin, which has been found to be effective in staphylococcal and streptococcal infections, was not considered pertinent to this study.

Aureomycin,† which is derived from a strain of *Streptomyces aureofaciens,*

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has been shown to possess, in vitro, antibacterial activity against numerous gram-positive and gram-negative bacteria. It appears to be bacteriostatic rather than bactericidal, except in high drug concentrations.

Chloromycetin,* which is obtained from filtrates of submerged aerated cultures of a Streptomyces sp., has been found to be quite effective against a number of rickettsiae, and several gram-negative bacteria. In vitro, crystalline chloromycetin has been found to be inactive against yeasts and filamentous fungi, inactive against protozoa, moderately active against gram-positive bacteria and Mycobacterium tuberculosis, and active against gram-negative bacteria and Borrelia recurrentis. Among the gram-negative organisms showing a considerable degree of sensitivity are the Brucellae, members of the salmonella group, and coliform bacteria.

TABLE I.—*Comparative Sensitivity of Organisms Commonly Found in Peritonitis of Appendiceal Origin.*

| Organism | Penicillin | Streptomycin | Aureomycin | Chloromycetin |
|---|---|---|---|---|
| *Staph. non hemolyticus*..... | Excellent | Moderate | Excellent | Moderate |
| *Str. viridans*, alpha..... | Excellent | Not susceptible | Excellent | |
| *Str. pyogenes*, beta..... | Excellent | Moderate | Excellent | |
| *Str. non hemolyticus*, gamma.. | Excellent | Moderate | Excellent | Good |
| *Escherichia coli*..... | Not susceptible | Good | Excellent | Moderate |
| *Clostridia*..... | Moderate | Not susceptible | | |
| *Proteus*..... | Not susceptible | Moderate | Not susceptible | Excellent |
| *Strept. faecalis*..... | Excellent | Good | Moderate | |

Both aureomycin and chloromycetin are well absorbed from the gastro-intestinal tract. There are no reports up to the present time of toxic manifestations resulting from the oral administration of chloromycetin. Aureomycin has low toxicity. Nausea and gastro-intestinal irritation, manifested by diarrhea, has been reported.

The influence of both is greatest on the rickettsiae and on the viral agents of the psittacosis-lymphogranuloma group. Their in vitro and in vivo range of activity closely approximates one another. However, unlike chloromycetin, most strains of gram-positive cocci, pneumococci and hemolytic streptococci are actively inhibited by aureomycin.

Woodward,[15] in a presentation at the General Session, American College of Physicians, March 30, 1949, reported the therapeutic effects of these two new antibiotics in typhoid fever, undulant fever, tularemia, scrub typhus, murine typhus, rocky mountain spotted fever, as well as epidemic typhus and Q fever. He believes that chloromycetin is clearly the drug of choice in clinical

* The chloromycetin used in this study was supplied by the Research Division, Parke, Davis & Company.

typhoid. In tularemia, he states that aureomycin is more effective than streptomycin. Chloromycetin has not been tried clinically in tularemia. Experimentally, it is less effective than streptomycin.

Aureomycin has been found to be of value in lymphogranuloma venereum, psittacosis and primary atypical pneumonia. Comparison in these conditions with chloromycetin awaits further clinical trial.

In comparing the range of bacterial sensitivity of aureomycin and chloromycetin with streptomycin and penicillin (Table I), it seemed that valuable data might be obtained by studying the individual effectiveness of each of these antibiotics in a mixed type of infection such as occurs in peritonitis. Since peritonitis, in dogs, is comparable to human peritonitis, it was decided to study the effects of each of the four enumerated antibiotics in an experimental study on this animal.

Peritonitis was produced by two methods in this investigation. One employed the technic introduced by Bower and co-workers, and as modified by Fauley and his associates; the second, which basically represents a second study, employed the technic suggested by Rothenberg, Silvani and McCorkle.[19] These will be described as Study I and Study II.

## STUDY I

Animals were selected at random from stray, mongrel adult dogs weighing from 15 to 20 pounds and excluding pregnant dogs, and dogs previously operated upon. The abdomen was shaved, scrubbed and painted with iodine and alcohol. Aseptic technic was rigidly observed. Under intravenous nembutal sodium anesthesia, the abdomen was entered through a right rectus incision and the appendix drawn into the wound. Mesenteric attachments were divided, and the appendiceal vessels were clamped, divided and ligated with silk. In order to minimize a tendency toward intussusception, the appendix was ligated 1 cm. from its base, with three coarse silk ties, rather than directly at its base. The distal half of the appendix was then traumatized with a crushing clamp, the viscera replaced, and the incision closed in layers with silk. No drains were used and no dressings applied. Immediately after operation, each animal received 50.0 cc. of castor oil by stomach tube.

No attempt was made to withhold food or water postoperatively, and no intravenous fluids were given. Temperature and leukocyte counts were determined every other day. Necropsy was performed on all fatalities shortly after death. All animals operated on are included in the series. The animals that survived were examined not earlier than 14 days after operation. Bacterial culture studies were made of peritoneal exudate in all animals. A combination of antibiotics was not used in any of the treated animals, although it was recognized that their effectiveness might have been enhanced thereby. The purpose of the study was to compare the results of the antibiotics individually. Penicillin was not used in Study I.

Ten animals were used as controls. Of these, eight died of acute diffuse

peritonitis, six of them within the first four days. Two animals recovered, a survival rate of 20 per cent.

Ten animals were treated with streptomycin, starting 24 hours postoperatively and continuing for eight days. The dosage was 75 mg. every six hours intramuscularly, a dosage equivalent of 300 mg. every 24 hours. Of these, four died of peritonitis, three of them within the first six days. Six animals recovered, a survival rate of 60 per cent.

Ten animals were treated with aureomycin, starting 24 hours postoperatively and continuing for eight days. The dosage was 100 mg. four times a day orally. Of these, only one animal died, this occurring as late as the ninth day. Nine animals recovered, a survival rate of 90 per cent.

Ten animals were treated with chloromycetin, starting 24 hours postoperatively and continuing for eight days. The dosage was 62.5 mg. every four hours orally. Of these, two animals died, one on the fourth day, and one on the eighth day. Eight animals recovered, a survival rate of 80 per cent.

TABLE II.—(*Study I*) *Comparison of the Survival Rate in the Treated and Untreated Animals.*

| | No. Dogs | 2-Day Survivals | 4-Day Survivals | 8-Day Survivals | 14-Day Survivals |
|---|---|---|---|---|---|
| Controls | 10 | 8 | 6 | 4 | 2 |
| Streptomycin | 10 | 10 | 8 | 6 | 6 |
| Aureomycin | 10 | 10 | 10 | 10 | 9 |
| Chloromycetin | 10 | 10 | 9 | 8 | 8 |

All animals were autopsied as soon after death as possible, and peritoneal exudate culture studies made. In addition, all dogs that survived 14 days were sacrificed and culture studies made. Five control animals showed a predominance of *Escherichia coli.* Eight animals treated with streptomycin showed *Escherichia coli,* while only four treated with aureomycin showed this organism. It is interesting to note that of ten animals treated with aureomycin, eight showed various types of proteus organisms. All ten animals treated with chloromycetin showed *Escherichia coli,* while only two showed proteus organisms.

The comparative survival rates of Study I are shown in Table II. The results of bacteriological studies* of peritoneal exudate are shown in Table III. Note that only five of the ten control animals showed *Escherichia coli,* while eight out of ten animals treated with streptomycin, and ten out of ten treated with chloromycetin showed this same organism. Four control animals revealed proteus organisms; only two each of those treated with streptomycin and chloromycetin showed proteus organisms, while eight out of ten treated with aureomycin showed this organism.

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STUDY II

Rothenberg *et al.* have suggested that a more effective method of producing peritonitis in dogs would be to combine excision of the spleen and omentum with the technic of Bower, Fauley *et al.* as described under Study I.

Under Study II, the same principles of technic were observed except for the following: (a) In addition to isolating and ligating the cecum, the spleen

TABLE III.—(*Study I*) *Incidence of Bacteria Cultures from Peritoneal Exudate of Dogs, with Experimental Peritonitis.*

| Organism | Incidence | Controls 10 Dogs | Streptomycin 10 Dogs | Aureomycin 10 Dogs | Chloromycetin 10 Dogs |
|---|---|---|---|---|---|
| *Escherichia col* | | 5 | 8 | 4 | 10 |
| Gamma *streptococcus* | | 4 | 5 | 3 | 3 |
| *Proteus* | | 4 | 2 | 8 | 2 |
| *Clostridia perfringes* | | 5 | 3 | 1 | 7 |
| *Staphylococcus albus* | | 4 | 0 | 0 | 1 |
| *Streptococcus viridans* | | 0 | 2 | 0 | 5 |
| Beta hemolytic *streptococcus* | | 1 | 2 | 0 | 5 |
| *Staphylococcus aureus* | | 2 | 0 | 0 | 0 |

and the omentum of each animal were excised; (b) Five animals were used in each series instead of ten, and the period of observation covered seven days instead of 14. This shorter period of observation was selected because we were interested in bacteriological studies of peritoneal exudate rather than survival rate. The survival study is shown in Table IV.

TABLE IV.—(*Study II.*) *Comparison of the Treated and Untreated Animals in Experimental Peritonitis. (Method as in Study I with addition of excision of spleen and omentum).*

| Group | 1st Day | 2nd Day | 3rd Day | 4th Day | 5th Day | 6th Day | 7th Day |
|---|---|---|---|---|---|---|---|
| Control | 5 | 5 | 4 | 4 | 3 | 3 | 3 |
| Streptomycin | 5 | 4 | 4 | 4 | 4 | 4 | 4 |
| Penicillin | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| Aureomycin | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| Chloromycetin | 5 | 5 | 5 | 4 | 4 | 4 | 4 |

Five animals were used as controls, of which three survived seven days. All five animals showed a generalized peritonitis at autopsy, and no tendency to wall off. Eight different types of organisms were cultured from the peritoneal exudate with a total incidence of 22 positive cultures.

In this same study (Study II) the effects of penicillin were observed, in addition to those of streptomycin, aureomycin and chloromycetin. All five animals treated with penicillin survived for seven days, and then were sacrificed. Two of these animals showed a diffuse peritonitis and three showed a well localized abscess without evidence of a diffuse peritonitis. Bacteriological studies of peritoneal exudate revealed four different strains of organisms. The total incidence of positive cultures was eight. Five of these showed a heavy

over-growth of *Escherichia coli*. This represents the maximum number of positive cultures possible to attain in this study for any specific organism.

Four animals treated with streptomycin out of a possible five survived seven days. Autopsy of the animal that did not survive showed a diffuse peritonitis. Of those that survived, one showed a diffuse peritonitis, and three showed localized abscess formation about the appendiceal stump without evidence of diffuse peritonitis. Bacteriological studies revealed four types of organisms with a total incidence of 11 positive cultures.

TABLE V.—(*Study II.*) *Postmortem Peritoneal Findings.*

| Group | Animals not Surviving 7 days | | Animals Surviving 7 days | |
|---|---|---|---|---|
| | Diffuse Peritonitis | Local Abscess | Diffuse Peritonitis | Local Abscess |
| Control | 2 | 0 | 3 | 0 |
| Streptomycin | 1 | 0 | 1 | 3 |
| Penicillin | 0 | 0 | 2 | 3 |
| Aureomycin | 0 | 0 | 2 | 3 |
| Chloromycetin | 1 | 0 | 4 | 0 |

All five animals treated with aureomycin survived seven days. Upon sacrificing, autopsy studies revealed two with a generalized peritonitis, and three with localized abscess without evidence of diffuse peritonitis. Four types of organisms were cultured with a total incidence of 11 positive cultures. This incidence is similar to that for streptomycin, although the strains of organisms cultured were different. Streptomycin and aureomycin each had only one positive culture for *Escherichia coli*.

TABLE VI.—(*Study II.*) *Organisms Cultured from Peritoneal Exudate of Treated and Untreated Animals.*

| Organism | Control | Strepto-mycin | Peni-cillin | Aureo-mycin | Chloro-mycetin |
|---|---|---|---|---|---|
| *Streptococcus hemolyticus* | 3 | .. | 1 | 2 | 1 |
| *Streptococcus non-hemolyticus* | 3 | .. | .. | .. | 3 |
| *Streptococcus viridans* | .. | 4 | .. | .. | .. |
| *Escherichia coli* | 4 | 1 | 5 | 1 | 3 |
| *Staphylococcus albus* | 2 | 3 | 1 | .. | 2 |
| *Clostridia* group | 5 | 3 | 1 | .. | 4 |
| *Proteus vulgaris* | 2 | .. | .. | 4 | 2 |
| *Streptococcus faecalis* | 2 | .. | .. | 4 | .. |
| Gram negative rod anerobe | 1 | .. | .. | .. | .. |

In the series of animals treated with chloromycetin, four out of five survived. The animal that did not survive showed a diffuse peritonitis. In addition, the four animals that were sacrificed at the end of seven days, also showed a diffuse peritonitis. Bacteriological studies of the peritoneal exudate were positive for six types of organisms with a total incidence of 15 positive cultures. *Escherichia coli* was cultured in three out of five instances, and *Proteus vulgaris* appeared twice.

The character of peritonitis found at autopsy is shown in Table V, and the results of bacteriological studies in Table VI.

## CLINICAL STUDIES*

Since making our preliminary report, additional data has been accumulated, indicating the clinical applicability of aureomycin from the surgical viewpoint.

Eleven patients, with an age range of one and one-half to 39 years with generalized peritonitis secondary to perforation of the appendix have been treated with aureomycin. *Escherichia coli* cultures were obtained in nine of the 11 cases. In the remaining two cases, positive cultures were obtained for beta-hemolytic streptococci and *Clostridium welchii* respectively. Each patient was surgically treated by the removal of the appendix. Drainage was established in all of these cases. There were no deaths. The average length of stay in the hospital was 14.9 days.

Two patients with localized peritonitis secondary to perforation of the appendix also were treated with aureomycin. The appendix was removed in each case, and the abscess drained. The ages were four years and 71 years respectively. The average stay in the hospital was 9.9 days.

One patient, age 52, with a ruptured sigmoid diverticulum and generalized peritonitis, was treated by cecostomy, drainage of the peritoneal cavity and aureomycin. Peritoneal cultures revealed micro-aerophilic *Streptococcus viridans*. This patient died on the eleventh postoperative day. In view of the subsequent culture, it is possible that aureomycin combined with penicillin would have been of greater value.

Three patients with clinical evidence of an acute inflammatory reaction in the peritoneal cavity were treated with aureomycin and non-surgical intervention. One patient subsequently had an interval appendectomy. The appendix showed definite evidence of having been perforated. The history in each instance suggested a diagnosis of acute appendicitis with spreading peritonitis. The objective findings supported this impression. A brief summary of these three cases follows.

**Case 1.** W. T., No. 21376. This was a colored male, age 4, admitted to the University Hospital on February 9, 1949, with a history of pain in the left lower abdomen of 2 days duration. The pain had been severe and cramplike in character and associated with vomiting. Enemas had been moderately effective, without evidence of blood or mucous.

Admission temperature was 101.2° F. and leukocyte count 11,500. There was muscle splinting of the entire abdominal wall with board-like rigidity in the left lower abdomen. Tenderness was extreme in the left lower quadrant, and moderate elsewhere. Peristalsis was audible over the entire abdomen, except in the left lower quadrant. Rectal examination confirmed the impression of a mass in the left pelvic region. A tentative diagnosis of an abscess in the left pelvic region was made.

He was immediately given 50 mg. of aureomycin intramuscularly, and then placed on a regimen of 25 mg. of aureomycin intramuscularly every 4 hours, supplemented with

* Grateful acknowledgment is made to Drs. William D. Lynn and Thomas G. Barnes, University Hospital, Baltimore, Maryland.

an oral dose of 500 mg. every 6 hours. At the end of 6 days, parenteral medication was discontinued and the oral dose of aureomycin was reduced to 250 mg. every 6 hours. This therapeutic level was continued for 3 days, following which aureomycin therapy was discontinued.

Thirty-six hours after admission, abdominal tenderness had disappeared except in the left lower quadrant. Fifty hours after admission, there was but slight tenderness in the left lower abdomen and a mass, which shortly after admission became well defined in this area, appeared to be regressing rapidly.

Fourteen days after admission, he was discharged from the hospital with negative physical findings.

On April 5, 1949, he was readmitted to the University Hospital for an elective exploratory laparotomy. During the interval of discharge and readmission, he had remained asymptomatic.

Exploratory laparotomy following this admission revealed a mobile caecum, pulled somewhat to the left. The appendix, which was about 4 cm. in length, extended transversely across the pelvic brim, and was adherent to the superior surface of the bladder and peritoneum of the left iliac region. Loops of ileum were adherent anteriorly. Adhesions were friable. No free pus was encountered. The middle third of the appendix was about 1 cm. in diameter, and contained a thick exudate. The appendix was removed, and the stump invaginated. Convalescence was entirely without event.

**Case 2.** W. R., No. 45179. A white male, age 30, was admitted to the University Hospital on March 6, 1949, complaining of lower abdominal pain of 11 hours duration. He had been under medical care since 1941 for chronic infectious hepatitis. At the time of his present admission, he was convalescent both from a recent exacerbation of hepatitis and a liver biopsy.

On admission, the patient was slightly icteric. His most recent liver function test revealed a direct van den Bergh of 4.8 and an indirect one of 4.5. Bromsulfalein 28 per cent at the end of 40 minutes. Total proteins were 6.30, with an A-G ratio of 4.20 to 2.10. Physical examination revealed tenderness in the left lower quadrant just to the left of the midline, as well as marked tenderness and muscle spasm in the right lower quadrant in the area of McBurney's point. Rebound tenderness was present. No masses were palpated. Admission temperature was 101° F.; leukocyte count 14,700. In view of the evidence of severe recurring hepatitis, conservative therapy was advocated. He was placed on an oral dosage of 500 mg. of aureomycin every 4 hours, and the abdomen was re-examined every hour. In 12 hours, the temperature had dropped to 99.8° F., and the leukocyte count to 10,900, and in 24 hours, the temperature was 98.0° F., with a leukocyte count of 8,850. Simultaneously, there was a dramatic amelioration of signs and symptoms in the abdomen.

Thirty-six hours after admission, the blood count was 7,650 with a normal temperature. He was discharged from the hospital on the fourth day after admission. Total dosage of aureomycin 8 Gm. which was not supplemented with other antibiotics or chemotherapeutic agents. Five week follow-up has revealed no sequela.

**Case 3.** M. W., No. 43960, a white female, age 56, was admitted to the University Hospital on January 15, 1949, with a history of pain in the lower abdomen of two days duration, which had become excruciating 6 hours prior to admission. The pain, which was cramplike in character, radiated from the right lower quadrant into the left lower quadrant. There was no history of constipation or vomiting.

Admission temperature was 100.8° F. and the leukocyte count 24,300. Urinalysis was negative. There was marked tenderness and rigidity in both lower quadrants of the abdomen, and moderate tenderness in the upper quadrants. Pelvic examination was negative, except for tenderness in the right pelvic region.

A diagnosis of peritoneal irritation, probably secondary to an acute appendix, was made. Exploratory laparotomy was advised but was refused by the patient.

She was given 300,000 units of penicillin immediately after admission. This was repeated in 12 hours.

Twenty-four hours after admission, her temperature was 101° F. and abdominal rigidity was more marked in the right lower quadrant. She persisted in refusing operation. Penicillin was discontinued and she was given 1 Gm. of aureomycin orally. This was followed by 500 mg. of aureomycin every 4 hours. Approximately 14 hours later, her temperature was 99.5° F. and leukocyte count was 17,000. She was subjectively improved. Abdominal tenderness had diminished.

Thirty-six hours after starting aureomycin therapy, a mass could be palpated in the right lower abdominal quadrant, about the size of an orange. On the third day of therapy, she was afebrile and asymptomatic. Abdominal tenderness had disappeared and the mass had reduced in size. Leukocyte count was 11,000. She was discharged two days later, completely asymptomatic, at which time the mass in the right lower quadrant had become poorly defined. Follow-up has not been possible.

## DISCUSSION

The evidence in Case 3 supported a diagnosis of a spreading peritonitis, for which exploratory laparotomy was indicated and advised. Following the patient's refusal of operation and lack of response to penicillin, she was placed on aureomycin. Crile has shown that response to penicillin in peritonitis takes three to four days, and Altemeier[24] has offered an explanation for this slowness of response. It is possible that the apparently rapid response to aureomycin is due to its ability to act against *Escherichia coli* as well as secondarily associated organisms.

A total of 13 patients with peritonitis, secondary to appendicitis, were treated by surgery and aureomycin, and three patients with presumptive evidence of peritonitis were treated by aureomycin alone, without a fatality.

In addition, three intractable urinary tract infections, each of which showed positive cultures for *Escherichia coli,* have been successfully treated with aureomycin. Two of the cases are included with Table VII, showing an analysis of the clinical results.

The third case occurred in a 60-year-old male following a left lower pelvic ureterolithotomy. During the course of a year he had repeated hospital admissions because of chills, fever, urinary frequency and urgency. During these admissions he had penicillin, streptomycin and sulfadiazine respectively, without appreciable influence. He was placed on a course of 250 mg. of aureomycin every four hours for eight days, after which bacteriological studies of the urine were negative. He has remained asymptomatic during a five month follow-up period.

Table VII shows the surgical conditions treated with aureomycin, and Table VIII, the types of bacterial organisms cultured.

Chloromycetin has not been given a clinical trial from the surgical viewpoint except in lymphogranuloma venereum. In this condition it will probably compare in value with aureomycin. Experimental data thus far obtained does

not warrant its clinical use in peritonitis. In infections involving proteus organisms, it should prove to be of merit.

Ochsner and Johnston[25] have estimated that in cases of appendiceal peritonitis treated conservatively, three-fourths will subside spontaneously without going on to abscess formation, and that in the remaining 25 per cent incision and drainage of the abscess will be necessary.

TABLE VII.—*Clinical Studies.*

| | No. Patients | Diagnosis | Av. Age | Av. Hospital Days | Results | Mortality |
|---|---|---|---|---|---|---|
| Non-operative Cases | 3 | Acute appendicitis | 30 | 5.66 | Excellent | 0 |
| Operative Cases | 2 | Acute perforated appendicitis, walled-off abscess | 44.5 | 9.9 | Excellent | 0 |
| | 11 | Acute perforated appendicitis, generalized peritonitis | 19.42 | 14.9 | Excellent | 0 |
| | 1 | Perforated sigmoid diverticulitis, generalized peritonitis | 52 | 11 | Cecostomy and drainage | Died |
| Post-Operative Genito-Urinary Infections | 1 | *E. coli* cystitis, gastric ulcer | 74 | 19 | Asymptomatic | Died from severe gastric hemorrhage |
| | 1 | *E. coli* cystitis and peritonitis, following uretero-sigmoidostomy | 72 | 39 | Excellent | 0 |
| Total | 19 | | 23.40 | 11.21 | | 10.5% |

Crile, in discussing a series of cases of peritonitis of appendiceal origin, reported 23 cases that were treated successfully with penicillin alone. Four days of therapy with penicillin was adequate to control the average case. Of the 23 cases reported, 20 subsequently had an interval appendectomy with confirmation of a gross perforation of the appendix.

TABLE VIII.—*Organisms Cultured from Clinical Cases.*

| Organism | *E. Coli* | *B. Hemolytic Strept.* | *Strept. Viridans* | *Cl. Welchii* |
|---|---|---|---|---|
| Number of cases..... | 10 | 2 | 1 | 1 |

It has been stated by several observers that *Escherichia coli,* in pure culture, is not a pathogenic organism, but is in reality a saprophyte, and that in mixed infections, the gram-positive cocci are the chief offenders. Since penicillin does not inhibit the growth of *Escherichia coli,* its effectiveness in peritonitis is probably due to its ability to control secondarily associated organisms.

Altemeier has shown that cultures of *Escherichia coli* or of *Bacillus pyocyaneus* have the property of destroying the activity of penicillin. This ability could well account for the fact that large doses of pencillin are required to

control gram-positive cocci when they are growing in a mixed infection associated with *Escherichia coli.*

The treatment of peritonitis of appendiceal origin with antibiotics should not be construed as a substitute for surgery. Our series of patients is too small to be of clinical significance. However, the experimental and clinical results obtained suggest that aureomycin has a protective mechanism in peritonitis of appendiceal origin. A combination of penicillin and aureomycin therapy should be extremely effective in the treatment of peritonitis of appendiceal origin in those conditions, where for one reason or another surgery is either contra-indicated or physical (environmental) conditions preclude its possibilities. As a dual adjunct in the surgical treatment of peritonitis of appendiceal origin, it should further reduce the present mortality rate. If sufficient aureomycin is given to destroy the *Escherichia coli,* it is possible that smaller doses of penicillin would be effective.

## SUMMARY AND CONCLUSIONS

1. The clinical applicability of chloromycetin and aureomycin is reviewed. The major field of their usefulness appears to be in the treatment of infections with rickettsiae and certain of the virus group, and gram-negative infections.

2. Experimental peritonitis has been produced in a series of dogs in an attempt to compare the protective significance of aureomycin and chloromycetin with streptomycin and penicillin.

3. Experimental animals in Study II treated with either streptomycin, penicillin or aureomycin showed a tendency to develop a localized peritonitis. Control animals and those treated with chloromycetin did not show this tendency.

4. Additional experimental studies with chloromycetin and in larger doses, should be made before its clinical trial in peritonitis of appendiceal origin.

5. Smaller doses of penicillin would probably be adequate in the treatment of mixed infections involving *Escherichia coli,* when combined with aureomycin.

6. Since aureomycin is extremely effective against *Escherichia coli,* as well as most strains of gram-positive cocci pneumococci and hemolytic streptococci, further studies may prove it to be the antibiotic of choice in the treatment of peritonitis of appendiceal origin.

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DISCUSSION.—DR. WILLIAM A. ALTEMEIER, Cincinnati, Ohio: Most surgeons agree that modern chemotherapy has been of great value in the treatment of acute septic peritonitis. There is, however, no agreement as to the most effective antibacterial agent. As yet, there is no specific treatment for peritonitis and successful management depends primarily on early diagnosis and prompt surgical intervention. A review of our clinical experience in a total of 1283 cases of acute secondary peritonitis during the past eight years reveals that the mortality was reduced approximately 60 per cent in the 598 cases treated with