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The Experimental and Clinical Use of Polymyxin, Chloromycetin, and Aureomycin

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SUMMARY

Polymyxin is an effective antibiotic for the treatment of severe infections produced by Ps. aeruginosa, H. pertussis, H. influenzae, E. coli, and A. aerogenes. Its toxicity to date precludes its general use in infections susceptible to its therapeutic effects.

Chloromycetin has been demonstrated to be an effective antibiotic agent for the treatment of rickettsial diseases and typhoid fever. It will undoubtedly prove effective in the treatment of other infections produced by certain Gram-negative micro-organisms and viral agents.

Aureomycin has been shown to be an active antibiotic agent against rickettsial diseases, primary atypical pneumonia, acute brucellosis, pneumococcal, streptococcal, and staphylococcal infections, urinary tract infections produced by E. coli, A. aerogenes and Strept. fecalis, certain types of infections of the eye, and in subacute bacterial endocarditis when the infecting agent is Strept. fecalis. Its clinical use in forms of extrapulmonary tuberculosis is in a completely experimental stage. It is not recommended in typhoid fever or in infections due to Ps. aeruginosa or P. vulgaris, and it seems to be ineffective in whooping cough.

To date, neither chloromycetin nor aureomycin has shown significant signs of systemic toxicity.

DURING the past 18 months, three new antibiotic agents, polymyxin,* chloromycetin,† and aureomycin,‡ have been described. The purpose of this presentation is to discuss certain observations which have been made regarding the antibacterial or bacteriostatic activity, the pharmacology and toxicity, the comparative effectiveness in experimental infections, and the potential clinical uses and value of these three compounds.

BACTERIAL AND BACTERIOSTATIC ACTIVITY

It can be said that, from the point of view of antibacterial activity, the polymyxins are definitely more effective *in vitro* than is streptomycin against certain Gram-negative bacteria. In our experience polymyxin D has from two to eighty times the activity of streptomycin against susceptible bacteria (see Table 1).

Furthermore, the activity of polymyxin is primarily bactericidal in the concentrations used, while that of streptomycin is bacteriostatic. Another point

*References 1, 4-6, 9-11, 26, 36, 46-48.
†References 3, 21, 32, 33, 40-44, 50, 53.
‡References 2, 7, 8, 12-20, 23-25, 27-31, 34, 35, 37-39, 45, 49, 51, 52.

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From the Department of Preventive Medicine, The Johns Hopkins University School of Medicine. These investigations were supported by grants from the Abbott Laboratories; Eli Lilly and Company; Lederle Laboratories Division, American Cyanamid Company; Parke, Davis and Company; The Upjohn Company; and the Antibiotic Study Section, Division of Research Grants and Fellowships, The National Institutes of Health, Public Health Service of the Federal Security Agency. Polymyxin D and aureomycin were furnished by the Lederle Laboratory Division, American Cyanamid Company. Polymyxin B was supplied by Burroughs-Wellcome Company and chloromycetin by Parke, Davis and Company.

TABLE 1.—*Comparison of Streptomycin, Polymyxin D, Penicillin G in Vitro*

Organism		Minimal Inhibitory Concentration (Gamma/cc.) Streptomycin	Poly. D
GRAM-NEGATIVE BACILLI			
E. coli	No. 4	6.25	.16
	No. 9	6.25	.16
E. communior	No. 14	2.5	.62
Citrobacter	No. 6	5.0	.62
Aerobacter	No. 10	>100	1.25
	No. 12	2.5	1.25
Friedlander	A	.62	.31
	B	5.0	.62
Pyocyaneus	Her.	25	1.25
	Cal.	100	2.5
	But.	100	2.5
	No. 16	50	2.5
Proteus	No. 11	5	>100
	No. 17	5	>100
	No. 18	5	>100
	Her.	12.5	>100
GRAM-POSITIVE COCCI			
Streptococcus:			
Beta Gr. A	C203	12.5	.008
D	Zymo	50	2.5
	22 A	50	2.5
Alpha fecalis	Bla.	50	2.5
	Twy.	10	2.5
Pneumococcus I	SVI	12.5	.016
	Baily	2	.012
Staphylococci:			
Aureus	Zeut.	12.5	.062
	Zorn.	2	.062
Albus	Heatly	2	.016

of interest is that the authors have been unable to produce resistant organisms by exposure to polymyxin over long periods of time. Chloromycetin and aureomycin exert bacteriostatic effects on certain Gram-positive and Gram-negative bacteria *in vitro*. In testing these effects, the comparison for Gram-positive organisms has been made with penicillin, while streptomycin has been used for comparison in the instance of the Gram-negative organisms. Aureomycin was found to be from four to sixteen times as active as was chloromycetin against streptococci, pneumococci, and staphylococci, and from ten to eighty times less effective than penicillin against these organisms except in the instance of streptococci belonging to Group D in Lancefield's classification. When Gram-negative organisms were tested, the bacteriostatic activity of aureomycin and chloromycetin were comparable, but generally less than the antibacterial activity of polymyxin (see Tables 2 and 3).

The exceptions to this statement are the relative effectiveness of chloromycetin again certain strains of P. vulgaris, and the almost total lack of activity of chloromycetin and aureomycin against strains of Ps. aeruginosa. Aureomycin has also been tested against 11 strains of organisms belonging to the Brucella group and has been an effective bacteriostatic agent after 72 hours in concentrations of 0.25 to 2.0 micrograms per ml. or less. Other investigators have reported that polymyxin[9, 46] has an antibacterial effect against A. aerogenes, S. typhosa, E. coli, K. pneumoniae, P. multocida, S. gallinarum, S. pullorum, and S. flexner; that chloromycetin[44] has a bacteriostatic action against S. schottmulleri, Shig. paradysenteriae (Sonne), B. mycoides, Borrelia recurrentis, Br. abortus, Br. suis, Br. melitensis, S. typhosa, H. pertussis, P. tularense, selected strains of Mycobacterium tuberculosis, V. hominis, and certain yeasts and filamentous fungi; and that aureomycin[24, 30, 31] has a similar effect against various strains of Salmonella, N. catarrhalis, N. gon-

TABLE 2.—*Comparison of Chloromycetin, Aureomycin, Polymyxin D in Vitro*

Organism		Minimal Inhibitory Concentration (Gamma/cc.) Chloro.	Aureo.	Poly D.
GRAM-NEGATIVE BACILLI				
E. coli	No. 4	5	5	.165
	No. 9	10	5	.156
E. communior	No. 14	5	5	.625
Citrobacter	No. 6	5	5	.625
Aerobacter	No. 10	5	5	1.25
	No. 12	5	2.5	1.25
Friedlander	A	1.25	1.25	.312
	B	5	5	.625
Pyocyaneus	Her.	>100	100	1.25
	Cal.	100	100	2.5
	No. 16	>100	100	.625
	But.	100	100	2.5
Proteus	No. 11	<3.1	.625	>100
	No. 17	12.5	50	>100
	No. 18	25	100	>100
	Her.	12.5	100	.....

TABLE 3.—*Comparison of Chloromycetin, Aureomycin, Penicillin G in Vitro*

Organism			Minimal Inhibitory Concentration (Gamma/cc.) Chloro.	Aureo.	Peni. G
GRAM-POSITIVE COCCI					
Streptococci:					
Beta Group	A	C203	5	.312	.008
	B	090	5	1.25	.016
	B	19	5	.625	.035
	C	K61	5	.625	.016
	D	Zymo.	10	1.25	2.5
	D	22A	10	.625	2.5
	F	For.	2.5	.625	.05
	F	H59	5	1.25	.016
Alpha fecalis		Bla.	10	1.25	2.5
		Tar.	10	1.25	2.5
		West.	10	1.25	2.5
Viridans		Dop.	5	.625	.625
		Keel.	10	.625	2.5
Pneumococcus I		SVI	2.5	.312	.016
Staphylococci:					
Aureus		Zeut.	5	.625	.062
		Zorn.	5	.625	.062
		Gelb.	5	.625	.062
		Gibb.	10	.625	.012
Albus		Heatly	5	.625	.012

orrheae, N. meningitidis, pleuropneumonia-like organisms, S. typhosa, H. hemolyticus, and certain other micro-organisms. Paine and co-workers[31] have reported that they have been able to produce resistance to aureomycin in certain strains of A. aerogenes and Kl. pneumoniae by repetitive cultivation in media containing the antibiotic, and the authors of this presentation have occasionally been able to produce a fourfold increase in the resistance to aureomycin of a strain of micro-organisms. However, such experiences are infrequent and of a low order, which makes the interpretation of their real meaning difficult. The conclusion has to be that it is difficult to produce resistance *in vitro* to aureomycin.

EXPERIMENTAL TOXICITY

Polymyxin D is moderately toxic for white mice, the LD_{50} being 250 to 300 mg. per kg. of body weight when the antibiotic is given by a single subcutaneous injection. Because of its relative insolubility, it is difficult to determine the LD_{50} of chloromycetin for mice. However, it has been reported that the LD_{50} of this compound in propylene glycol is 245 mg. per kg. when it is administered to white mice by the intravenous route. For aureomycin, the LD_{50} for white mice was found to be 3,500 mg. per kg. when this antibiotic was given by the subcutaneous route. In larger animals, such as dogs, 10 mg. of polymyxin D per kg. injected twice a day by the intramuscular route for seven days was well tolerated. With chloromycetin, dogs receiving from 72 to 80 mg. per kg. per day by the intramuscular route for 38 doses (five days a wek) developed varying degrees of anemia during the period of the test, while dogs receiving 40 mg. per kg. per day of aureomycin for nine days by the intramuscular route showed signs of anorexia and loss of weight. Because the hydrochloride of aureomycin, which is quite acid, was used in these tests, varying degrees of local necrosis were noted in these experimental animals. Neither polymyxin, nor aureomycin, nor chloromycetin produced any significant changes in the leukocyte counts, blood sugar, or liver function tests in the experimental animals. All samples of polymyxin tested to date have produced albumin, casts, leukocytes and erythrocytes in the urine of rats which had received polymyxin intravenously in daily dosage of 20 mg. per kg. Histological examinations of the kidneys of such rats show definite evidence of lower nephron damage. Certain specimens of polymyxin have produced symptoms and signs of histamine shock when injected into rats by the intramuscular route. It is possible that these reactions resulted from impurities in the material under test.

PHARMACOLOGY

Polymyxin D passes readily into the blood stream following its intramuscular injection into dogs. Ninety minutes after dogs had received single intramuscular doses of 5 or 10 mg. per kg., concentrations of 2.5 and 5.0 micrograms of polymyxin per ml. were recorded. Detectable amounts of the antibiotic were still present in the serum at three and one-half hours. When dogs were given 5 or 10 mg. of the compound per kg. twice daily for seven days, concentrations of from 10 to 20 mg. of polymyxin per ml. of serum were noted. No polymyxin was detected in the spinal fluid of dogs in which high concentrations of polymyxin were present in the serum. When polymyxin was administered to human beings in divided doses by the intramuscular route at intervals of three hours in amounts not to exceed a total daily dose of 3 mg. per kg. of body weight, concentrations of 0.6 to 1.3 micrograms of the antibiotic per ml. were noted in the sera after 24 hours of therapy. Detectable amounts of the antibiotic were present in the urine of these patients. To date it has not been found in the spinal fluid of patients suffering from purulent meningitis and treated with this antibiotic.

Aureomycin deteriorates quite rapidly when placed in solution. It is also bound by the proteins of blood serum in varying degrees. Hence, when biological testing against a strain of susceptible micro-organism is used for determining concentrations of this antibiotic in body fluids, the method is fraught with error. The same is also true when bacteriostatic tests are done. The figures obtained do not represent true values but rather qualitative instead of quantitative results. With this in mind, the following data are presented: When dogs and rabbits were injected with single doses of 20 or 40 mg. of aureomycin by the intramuscular route, concentrations of slightly over 1 microgram of the antibiotic per ml. were noted in the serum within one hour but not after that time. In a dog receiving 20 mg. of aureomycin per kg. of body weight twice a day for ten days, the antibiotic could be detected in the serum up until two and one-half hours after each injection. While the antibiotic was not observed in the spinal fluid, it did appear in quantity in the urine. When aureomycin was administered orally to human beings in doses of 500 mg. twice a day and 40 mg. every six hours by injection, concentrations of from 0.6 to 2.4 micrograms of the antibiotic per ml. were observed in the sera one hour after the injection was given. The antibiotic produces a greenish yellow discoloration of the urine, in which concentrations of from 40 to 360 micrograms per ml. have been observed.

Chloromycetin[44] appears promptly in the blood after the administration of a single oral dose or an intramuscular injection of this antibiotic. It also would appear that it is excreted fairly rapidly in the urine in which its recovery (as measured by biological tests) is fairly high. In experiments in which chloromycetin was administered to dogs over a period of 24 days by the oral or intramuscular route, concentrations of from 1 to 29 micrograms of chloromycetin per ml. of serum were noted two hours after treatment, and concentrations of 1 to 2 micrograms per ml. of serum, 18 hours after treatment. Concentrations of from 36 to 406 micrograms per ml. of urine were noted in these dogs. It was also deter-

mined that chloromycetin was bound to the proteins of the serum to the extent of about 45 per cent. In patients ill with typhoid fever,[50] and treated with initial daily doses of between 4 and 5 gm. of chloromycetin, concentrations of from 40 to 80 micrograms per ml. were noted in the serum within the first 24 hours of treatment. It was also observed that the concentration of chloromycetin in the spinal fluid was approximately half that noted in the blood.

TREATMENT OF EXPERIMENTAL INFECTIONS

Polymyxin has been shown to be an effective chemotherapeutic agent in the treatment of experimental infections in mice produced by K. pneumoniae, Type A (Friedlander's bacillus),[5, 11, 46] H. influenzae,[6] P. multocida,[46] and Shigella gallinarum.[46] In our laboratory it appeared to be from five to ten times more effective in the control of infections produced in mice by K. pneumoniae and H. influenzae than is streptomycin.

Chloromycetin has been shown to have a chemotherapeutic effect in experimental infections produced by rickettsia,[14, 21] K. pneumoniae, Type A,[44] Shigella paradysenteriae Sonne,[44] D. pneumoniae,[44] Strept. hemolyticus and Strept. viridans,[44] and certain viruses of the psittacosis group.[44] Wong and Cox[49] demonstrated that aureomycin is an effective chemotherapeutic agent in the treatment of experimental infections produced by various types of rickettsia. SubbaRow and his co-workers[24] have shown that this antibiotic cured experimental infections in mice produced by hemolytic streptococci, pneumococci, or K. pneumoniae, Type A. Heilman[25] has reported that aureomycin was effective against experimental infections produced by Borrelia novyi or Leptospira icterohemorrhagiae (see Tables 4, 5 and 6).

In tests made in our own laboratory of the comparative therapeutic effects of chloromycetin, aureomycin, polymyxin D, and penicillin in certain experimental infections in mice, the following results were obtained: As will be noted from a perusal of Table 4, in experimental infections in mice produced by the injection intraperitoneally of 10,000 M.L.D. of K. pneumoniae, Type A, aureomycin and chloromycetin showed essentially equal therapeutic activity. Both were about a hundred times less effective at the dosage levels employed than was polymyxin. As is shown in Table 5, in the treatment of experimental infections in mice produced by the intraperitoneal injection of 10,000 M.L.D. of Strept. hemolyticus (strain C203), aureomycin appeared to be about 25 times more effective than chloromycetin, and about ten times less effective than was crystalline penicillin G. When mice were infected with 10,000 M.L.D. of D. pneumoniae, Type I (strain SVI), and then treated (Table 6), aureomycin was over 40 times more effective as a therapeutic agent than was chloromycetin, and about five times less effective than was crystalline penicillin G. In these tests only an approximate comparison could be made between aureomycin and chloromycetin because of the relative insolubility of the latter compound. In making these studies of therapeutic effectiveness, the mice were treated by the subcutaneous route, immediately, at five hours, and then at 23 hours after they had been infected. They were observed for six days after therapy had been discontinued.

TREATMENT OF INFECTIONS IN HUMAN BEINGS

There can be no doubt as to the therapeutic effectiveness of polymyxin for the treatment of local and systemic infections produced in human beings by certain Gram-negative bacilli. Outstanding among the infections which have responded to treatment with this antibiotic have been those due to Ps. aeruginosa, K. pneumoniae, H. pertussis, H. influenzae, Type B, and E. coli. In severe instances of infection which were treated by the intramuscular injection of

TABLE 4.—*Comparison of the Effects of Aureomycin, Chloromycetin and Polymyxin D in Friedlander Infection in Mice*

Friedlander A—10,000 M.L.D. Injected I.P.—10 Mice Each Group

Dose Gamma/Gram	Per Cent Survival Aureo.	Chloro.	Poly. D	Controls
80	80	90	....	....
25	10	10	....	....
8	0	0	....	....
4	....	....	80	....
1.25	....	....	90	....
0.4	....	....	50	....
0	....	....	....	0

(Drug Administered S.C., Stat., 5 and 23 Hours After Infection)

TABLE 5.—*Comparison of the Effects of Aureomycin, Chloromycetin and Penicillin G in Hemolytic Streptococcal Infection in Mice*

C203 Strain—10,000 M.L.D. Injected I.P.—10 Mice Each Group

Dose Gamma/Gram	Per Cent Survival Aureo.	Chloro.	Peni.G	Controls
50	....	30	....	....
10	....	0	....	....
2	50	0	....	....
1	0	....	....	....
0.5	0	....	....	....
0.2	....	....	40	....
0.1	....	....	0	....
0.05	....	....	0	....
0	....	....	....	0

(Drug Administered S.C., Stat., 5½ and 23 Hours After Infection)

TABLE 6.—*A Comparison of the Effects of Aureomycin, Chloromycetin and Penicillin G in Experimental Pneumococcal Infections (SVI Type I Pneumococcus)*

10,000 M.L.D. Inocula. I.P.—10 Mice Each Group

Dose Gamma/Gram	Per Cent Survival Aureo.	Chloro.	Peni.G	Controls
20	90	0	....	....
8	30	0	....	....
5	....	....	80	....
2	10	0	60	....
0.8	....	....	10	....
0	....	....	....	0

(Drug Administered S.C., Stat., 5 and 23 Hours After Infection)

polymyxin at three-hour intervals, the results frequently have been very satisfactory. As an example, the course of a patient deathly ill as a result of a systemic infection produced by Ps. aeruginosa will be outlined. This man had been treated with sulfadiazine, penicillin, and streptomycin without beneficial results. At the time therapy with polymyxin D was initiated, the patient was deeply jaundiced, there was consolidation of the left lung, a bacteriological culture of the blood was positive, and, in the opinion of several competent clinicians, he was moribund. The effect of treatment with polymyxin was more than dramatic, as the patient was well on the road to recovery within 24 hours after therapy was started.

The total daily dose of polymyxin D has been based upon 3 to 6 mg. of the antibiotic per kg. of body weight, this being split into six equal doses and given in a special buffer solution (pH 7.4) at intervals of four hours. It is indeed unfortunate that the toxicity (as will be described later) of the various specimens of polymyxin which have been tested to date is such as to preclude the general use of this antibiotic. However, it must be said that in severe instances of systemic or localized infections due to Ps. aeruginosa, K. pneumoniae, A. aerogenes, H. pertussis, etc., the authors would not hesitate to employ polymyxin D as a therapeutic agent in cases in which the dangers of the disease outweighed those of temporary renal damage. This antibiotic may be life-saving.

Chloromycetin has been shown to be a highly effective therapeutic agent in the treatment of epidemic typhus,[32] scrub typhus,[43] Rocky Mountain spotted fever, eastern variety,[33] and typhoid fever.[50] Payne and his associates[32] have reported that chloromycetin in doses of 10 mg. per kg. of body weight per day given by the intravenous route, or 15 mg. per kg. of body weight per day given by the oral route for a period of three days, was effective in the treatment of epidemic typhus fever. Smadel and co-workers[43] have described the treatment of scrub typhus with this antibiotic. In 25 patients with this disease, the administration of chloromycetin in varying doses brought about a prompt cure. Doses as small as 6.0 gm. of chloromycetin given for *one day* produced satisfactory responses. Pincoffs and his co-workers[13] have tested the effects of chloromycetin in 15 patients ill with Rocky Mountain spotted fever, eastern variety. Here again, excellent results were obtained in all patients who were treated. Finally, Woodward, Smadel, Ley, Green, and Manikas[50] have found that chloromycetin administered by mouth in initial doses of 50 mg. per kg. and continuing doses of 0.25 gm. every two hours until the temperature was normal, and then in the same dose every three or four hours for the ensuing five days, exerted a specific therapeutic effect in ten patients ill with early typhoid fever, all of whom had at least one blood culture positive for S. typhosa before treatment was started. The average time in which the temperature returned to normal in these ten patients was three and one-half days. As chloromycetin has been in short supply, the authors have had little clinical experience with this antibiotic. It would appear very clear, however, that it is an extremely effective antibiotic for the treatment of rickettsial diseases, its use in typhoid fever seems established, and from experimental observations *in vitro* and *in vivo* it is likely that it will prove to be an effective chemotherapeutic agent in infections produced by certain Gram-negative organisms and viral agents.

It has been reported[33, 36] that aureomycin appeared to be an effective chemotherapeutic agent in the treatment of Rocky Mountain spotted fever, eastern variety, certain urinary tract infections produced by E. coli, A. aerogenes, or Strept. fecalis, acute and subacute undulant fever, primary atypical pneumonia, and staphylococcal infections. Recently Braley and Sanders[7, 8] have stated that this antibiotic is valuable in the treatment of staphylococcal conjunctivitis and blepharitis, influenzal conjunctivitis, pneumococcal conjunctivitis, inclusion conjunctivitis, early epidemic keratoconjunctivitis, dendritic keratitis, vernal conjunctivitis, and Mooren's ulcer. The agent was without effect in Piranaud's conjunctivitis and in late cases of epidemic keratoconjunctivitis. Wright and his co-workers[51, 52] believe that aureomycin "is the treatment of choice in all cases of lymphogranuloma infection." They also recommend further study of the effect of the drug in granuloma inguinale because of three favorable results which were obtained with it in patients ill with this disease. The results relative to granuloma inguinale have been confirmed by Greenblatt and co-workers[23] who reported excellent results when this antibiotic was used in three cases in which the disease had proven resistant to treatment with streptomycin.

Finland and his associates[16, 22] have reported that aureomycin exerted a beneficial effect in certain coccal infections, although in gonococcal infections the results were inferior to those which could be expected with penicillin. In Salmonella infections, the results were equivocal, while in urinary tract infections the effects of therapy were good, except in patients whose infections were produced by P. vulgaris or Ps. aeruginosa. Spink and co-workers[45] have used aureomycin in patients ill with acute and chronic brucellosis produced by infection with Br. melitensis. They state that "the immediate therapeutic results have surpassed those obtained with any therapy, including a combination of streptomycin and sulfadiazine." Lennette, Meiklejohn, and Thelen[27] tested the effects of aureomycin given by mouth in the treatment of Q fever. Prompt response to therapy was noted in 14 patients acutely ill with this disease. In one patient, in whom the disease was present in a chronic form, the antibiotic seemed to be ineffective. O'Leary, Kierland, and Herrell[29] have reported that "aureomycin appears to have some antispirochetal activity when administered by the oral route." This observation upon the effects was noted when the antibiotic was used in the treatment of two patients who had early syphilis.

To these observations may be added a report on

further clinical experiences with aureomycin at Johns Hopkins Hospital. Sixteen patients ill with Rocky Mountain spotted fever, eastern variety, with the disease proven by serological methods in 13 of them, were treated with aureomycin. The details of this clinical experience have been recently described by Ross and co-workers.[35] The results obtained were excellent in all instances. Treatment with aureomycin was begun an average of 4.5 days after onset of symptoms. The temperature returned to normal in an average of 2.3 days after treatment was started. There were no complications. The average period of hospital stay was eight days. Experience with one patient is charted in Chart 1. One patient who was severely ill with Brill's disease was treated with prompt and excellent results, as was also one patient suffering from acute Q fer.

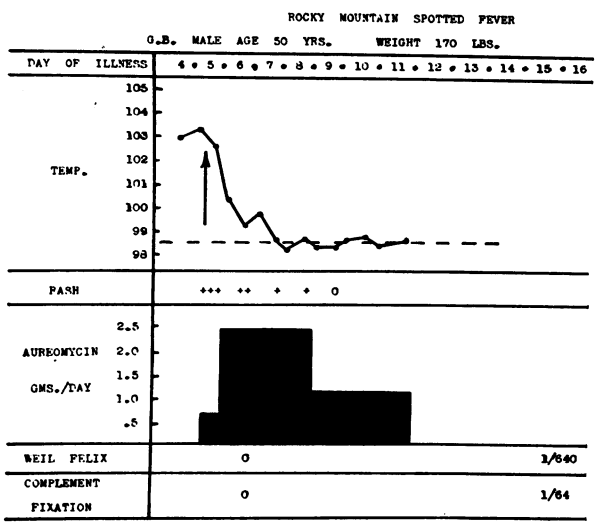

Chart 1

In 17 cases in which, by all available methods of exclusion, a diagnosis of primary atypical pneumonia was made, the patients were treated with aureomycin with excellent results. In 13 cases the temperature of the patient was normal in 24 hours, and in three within 48 hours. In one case in which four lobes were involved in the disease process, the patient was afebrile in 72 hours. All patients experienced prompt symptomatic relief and the pneumonic processes in the lungs cleared up rapidly after treatment was initiated. The details of this clinical experience are being reported by Schoenbach and Bryer.[39] Experience in one case is summarized in Chart 2.

Five patients ill with acute or subacute brucellosis, in all of whom positive blood cultures were obtained, were treated with aureomycin. In four of these patients the infection was due to Br. suis, while in the other Br. abortus was recovered from the blood. All had symptoms typical of the disease and four had enlarged spleens. The titer of antibody

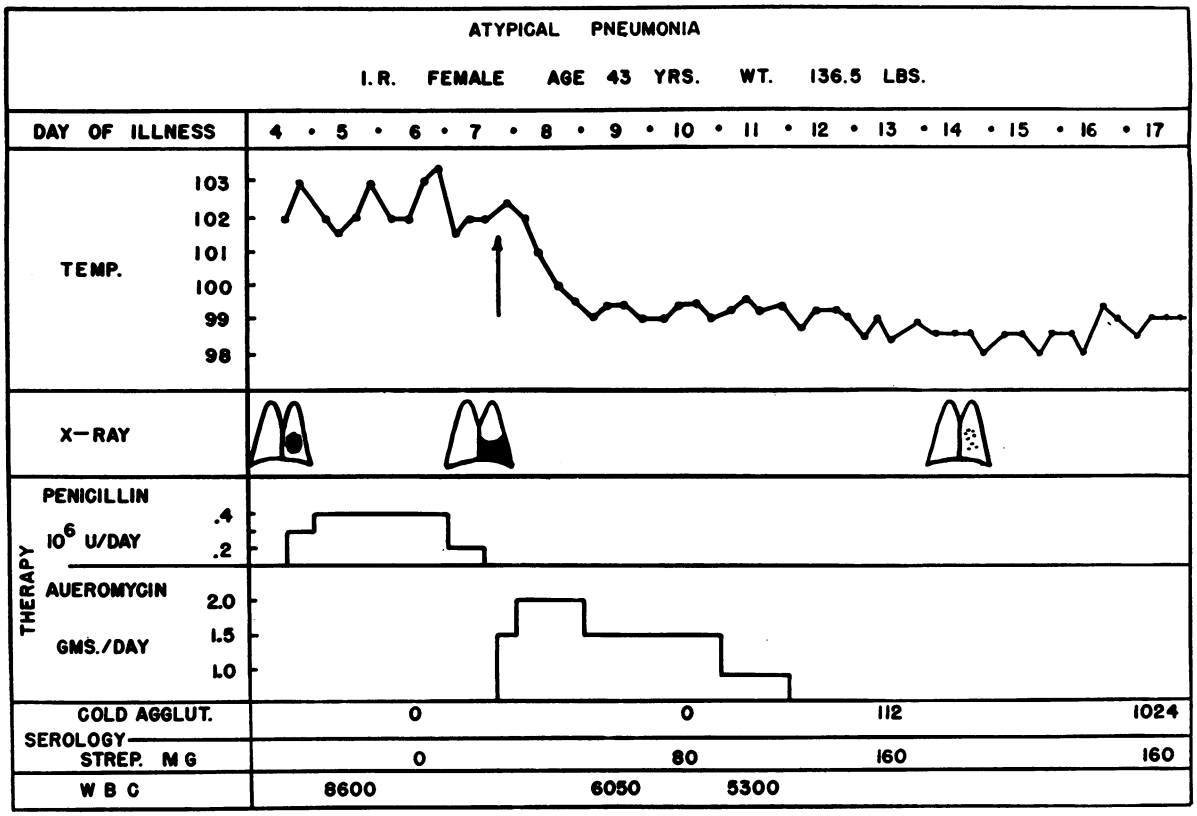

Chart 2

for the specific strain of the Brucella group with which they were infected was high in the serum of each patient. One had not been cured by previous treatment with sulfadiazine, streptomycin and sulfadiazine, and polymyxin, while another had had an ineffectual course of streptomycin and sulfadiazine. In all five patients there was dramatic clinical response to the administration of aureomycin, with the temperature falling to normal within 72 hours and with a progressive remission of all symptoms and signs. Treatment was carried out over a 14-day period. These patients have been followed from three to seven months. All have gained weight consistently and none has shown symptoms or signs of a return of the disease. The details of this experience are being reported by Bryer and his associates.[13] Experience in one case is shown in Chart 3.

Six patients with various forms of tuberculosis were treated with aureomycin. In three, who had tuberculous meningitis, the antibiotic was not effective. In the case of a 12-year-old Negro girl who had had five scrofulous sinuses in the neck for seven years, from each of which tubercle bacilli had been repeatedly isolated in guinea pigs, the administration of aureomycin for six weeks resulted in the closure of all sinuses a week after treatment had been started and, to date, there has been no recurrence of the disease. The fifth patient had advanced tuberculosis of the renal tract with marked involvement of the bladder. One kidney had been removed because of the infection. This patient has been under treatment for three months and has had a remission of the symptoms and signs of the disease. Treatment is being continued, however. A sixth patient ill with cavitating tuberculosis was treated for two weeks with aureomycin without evidence of clinical improvement. At the time of this writing it must be made very clear that no claims are being made for the therapeutic use of aureomycin in tuberculosis. This is merely a report of observations.

Five patients with typhoid fever were treated with aureomycin. While all recovered and in all cases blood and stool cultures became negative soon after antibiotic therapy had been instituted, the results as far as the decline in the fever and the general improvement of the patient were concerned were equivocal and might well have been due to chance. Chloromycetin would appear to be definitely superior to aureomycin for the treatment of this disease.

Eighteen patients with serious and complicated infections of the urinary tract were treated with aureomycin. All had previously received sulfonamides, penicillin or streptomycin, or a combination of them. All had anatomical or functional abnormalities of the urinary tract. The infecting organisms were E. coli, A. aerogenes, or Strept. fecalis or a mixture of two or more of these micro-organisms. The immediate effects from therapy were satisfactory in 17 and fair in one of these patients. It remains to be seen what the long time results

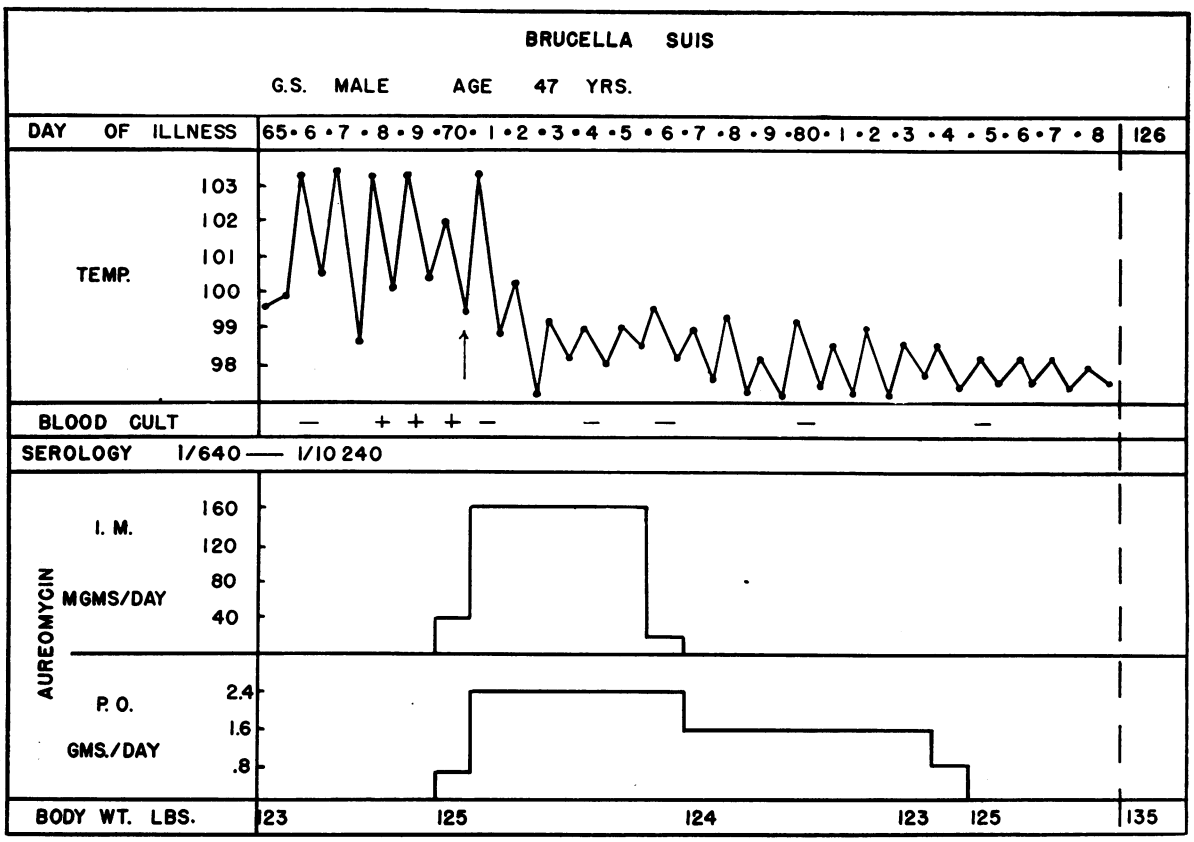

Chart 3

will be. Aureomycin is ineffective in urinary tract infection with Ps. aeruginosa or P. vulgaris.

Eight patients ill with moderate to severe infection with Staph. aureus hemolyticus, in two of whom staphylococcal bacteremia was present, were treated with aureomycin. In several of these patients antecedent therapy with sulfadiazine and/or penicillin had been unsuccessful. In seven of the eight patients prompt and satisfactory response to therapy was noted. In the eighth, an infant whose initial infection was staphylococcal pyodermia, extensive signs of pulmonary involvement were present despite continuous therapy with penicillin for a period of more than two months. When treatment with aureomycin was initiated, the pulmonary signs cleared rapidly except for one small area. After two weeks of therapy with aureomycin, material for culture was obtained from this area by bronchoscopic examination, and a strain of Staph. aureus hemolyticus, which was resistant *in vitro* to more than 100 micrograms of aureomycin per ml., was isolated. This patient now is clinically well. These experiences are being reported by Chandler, Schoenbach, and Bryer.[15]

Whenever a new antibiotic is being tested clinically, a number of patients with infections for which there is no experimental evidence for the use of the antibiotic must be treated with it, if only to maintain harmony in the society of physicians. Certain of these patients which we will place in the category of "miscellaneous infections" will be discussed. Among the patients with miscellaneous infections which experimental evidence indicated might be abated by use of aureomycin, were the following: One patient ill with meningitis produced by Strept. fecalis, was promptly cured by the oral administration of aureomycin. One patient ill with pneumococcal meningitis produced by D. pneumoniae, Type 6, had been treated with sulfadiazine and penicillin, and the infecting organism had become resistant to these therapeutic agents. Cultures of the spinal fluid were abundantly positive for D. pneumoniae before therapy with aureomycin was initiated. Recovery was prompt after this antibiotic had been administered. One patient, a child who had subacute bacterial endocarditis, with four cultures positive for Strept. fecalis, was treated with aureomycin by mouth for a period of two weeks with excellent results. Four months later this child seemed to be in good health. Another patient with the same disease, with blood cultures repeatedly positive for Strept. fecalis, was treated with excellent initial results insofar as abatement of fever and other signs and symptoms are concerned. However, the follow-up period is not yet long enough for the patient to be considered cured. Two patients who had brain abscesses, one due to Staph. aureus hemolyticus and the other to E. coli, have been treated with satisfactory results. Two patients ill with generalized peritonitis, with the infection in one case produced by E. coli and Strept. fecalis, and by Strept. fecalis in the other, have been successfully treated with aureomycin. In both instances the response to therapy was dramatic, and in both aureomycin was used after surgical therapy had not brought about the desired results. Aureomycin was given to two patients having definite signs of localized postoperative infections. In one the infection followed resection of a carcinoma of the colon with an end-to-end anastomosis of the bowel which broke down and resulted in a fecal sinus; in the other there was a persistent purulent abdominal sinus following drainage of a pelvic abscess. In both there was prompt remission of signs and symptoms together with a closure of the sinuses following therapy with aureomycin. In both instances the infecting organisms were E. coli and Strept. fecalis. Two patients ill with whooping cough did not respond to treatment with aureomycin. One patient each with polioencephalitis, noma, and pancreatic necrosis with secondary infection have been treated without results. The same is true of four patients ill with erythema multiforme.

ADMINISTRATION AND DOSAGE

Up to the present, oral administration is the method of choice for aureomycin. No satisfactory preparation for general intravenous use has been developed so far. The antibiotic, as supplied, is a hydrochloride salt, and when this is administered intramuscularly it produces pain due to the acidity of the product. This has militated against its use by this route. It is too early in the history of aureomycin to establish accurate dosage schedules for the administration of this antibiotic. It is likely that the dosage schedules recommended herein will eventually be proven to have been excessive. However, they have been effective. In severely ill patients who are being treated orally, the total daily dose of aureomycin should be based on 60 mg. per kg. of body weight. Initial "priming" doses equivalent to one-sixth of the total daily dose should be given to seriously ill patients at hourly intervals for three doses. Then one-sixth of the estimated daily dose should be given at intervals of four hours until the temperature has been normal for 24 hours. At this time the basis for the total daily dose should be reduced by one-half or to 30 mg. per kg. of body weight. This should be divided into four parts and given at intervals of six hours until the infection is eliminated. In moderately severe infections the total daily dose should be based on 30 mg. per kg. of body weight, this to be divided into four or six equal parts and given at intervals of six to four hours until the infection is under control. As approved derivatives of aureomycin for parenteral injection are not available, use of the drug by this route will not be discussed.

CLINICAL TOXICITY

Polymyxin, being a polypeptide or a mixture of polypeptides, should not produce toxic reactions as the result of the sensitization of the patient to the antibiotic. This has been true in the author's experience thus far. All specimens of this antibiotic which we have tested have produced varying degrees of renal tubular dysfunction. In the mildest form it

appears as a fixation of the specific gravity of the urine, while in severe forms, oliguria with albumin, casts, erythrocytes and leukocytes in the urine, and elevated non-protein-nitrogen levels and depressed renal function may occur. These latter reactions sometimes become very disturbing and it is because of them that the general use of polymyxin seems contraindicated. Histamine-like reactions, hypasthesias, and fever have been noted in the course of polymyxin therapy, but these reactions would appear to be due to impurities in the specimens of polymyxin which were being used rather than to the antibiotic itself.

Neither aureomycin nor chloromycetin has shown significant evidence of clinical toxicity up to the present. This is extremely interesting, because, despite the fact that both of these products are derived from members of the family of Streptomyces, reports of sensitization or other toxic reactions have not been made, and this in face of the fact that several hundred patients have been treated with these antibiotics. Some nausea has been reported by patients receiving aureomycin, but this generally can be controlled by the administration of preparations containing aluminum hydroxide. The passage of two or three bulky stools per day is frequently reported by patients who are taking aureomycin. This change in the stool is apparently due to an alteration in, or wiping out of, the normal bacterial flow of the large bowel. As this may interfere with the synthesis of essential food elements, it may be advisable to administer supplementary vitamins to patients who are receiving aureomycin for periods longer than a week.

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REFERENCES

1. Ainsworth, G. C., Brown, A. M., and Brownlee, G.: "Aerosporin" an antibiotic produced by Bacillus aerosporus greer, Nature, London, 160:263 (Aug. 23), 1947.

2. Anigstein, L., Whitney, D. M., and Beninson, J.: Aureomycin—A new antibiotic with anti-rickettsial properties; its effect on experimental spotted fever and epidemic typhus, Ann. N. Y. Acad. Sci., 51:306 (Nov.), 1948.

3. Bartz, Q. R.: Isolation and characterization of chloromycetin, J. Biol. Chem., 172:445 (Feb.), 1948.

4. Benedict, R. G., and Langlykke, A. F.: Antibiotic activity of Bacillus polymyxa, J. Bact., 54:24 (July), 1947.

5. Bliss, E. A., Chandler, C. A., and Schoenbach, E. B.: *In vitro* studies of polymyxin, Bull. Johns Hopkins Hosp., 82:635 (June), 1948.

6. Bliss, E. A., Chandler, C. A., and Schoenbach, E. B.: *In vitro* studies of polymyxin, Ann. N. Y. Acad. Sci., in press.

7. Braley, A. E., and Sanders, M.: Aureomycin in ocular infections, Ann. N. Y. Acad. Sci., 51:280 (Nov.), 1948.

8. Braley, A. E., and Sanders, M.: Aureomycin in ocular infections, J.A.M.A., 138:426 (Oct. 9), 1948.

9. Brownlee, G., and Busby, S. R. M.: Chemotherapy and pharmacology of aerosporin, Lancet, I:127 (Jan. 24), 1948.

10. Bryer, M. S., Schoenbach, E. B., Bliss, E. A., and Ott, C. E.: The experimental toxicology, pharmacology, and effectiveness of polymyxin, Bull. Johns Hopkins Hosp., 82:636 (June), 1948.

11. Bryer, M. S., Schoenbach, E. B., and Bliss, E. A.: The pharmacology of polymyxin, Ann. N. Y. Acad. Sci., in press.

12. Bryer, M. S., Schoenbach, E. B., Chandler, C. A., Bliss, E. A., and Long, P. H.: Aureomycin, experimental and clinical investigations, J.A.M.A., 138:117 (Sept. 11), 1948.

13. Bryer, M. S., Schoenbach, E. B., Wood, R. M., and Long, P. H.: The treatment of acute brucellosis with aureomycin, Bull. Johns Hopkins Hosp., in press.

14. Chandler, C. A., and Bliss, E. A.: *In vitro* studies with aureomycin, Ann. N. Y. Acad. Sci., 51:221 (Nov.), 1948.

15. Chandler, C. A., Schoenbach, E. B., and Bryer, M. S.: The treatment of acute staphylococcal infection, in press.

16. Collins, H. S., Paine, Jr., T. F., and Finland, M.: Clinical studies with aureomycin, Ann. N. Y. Acad. Sci., 51:231 (Nov.), 1948.

17. Cooke, C.: Aureomycin, J.A.M.A., 138:885 (Nov. 20), 1948.

18. Dornbush, A. C., and Pelcak, E. J.: The determination of aureomycin in serum and other body fluids, Ann. N. Y. Acad. Sci., 51:218 (Nov.), 1948.

19. Dowling, H. F., Lepper, M. F., Sweet, L. K., and Brickhouse, R. L.: Studies on serum concentrations in humans and preliminary observations on the treatment of human infections with aureomycin, Ibid., 241.

20. Duggar, B. M.: Aureomycin, a product of the continuing search for new antibiotics, Ibid., 177.

21. Ehrlich, J., Bartz, Q. R., Smith, R. M., Joslyn, D. A., and Burkholder, P. R.: Chloromycetin, a new antibiotic from a soil actinomycete, Science, 106:417 (Oct. 31), 1947.

22. Finland, M., Collins, H. S., and Paine, Jr., T. F.: Aureomycin, a new antibiotic, J.A.M.A., 138:947 (Nov. 27), 1948.

23. Greenblatt, R. B., Dienst, R. B., Chen, C., and West, R.: Oral aureomycin therapy in the therapy of streptomycin-resistant granuloma inguinale, Sou. Med. J., 41:1121 (Dec.), 1948.

24. Harned, B. K., Cunningham, R. W., Clark, M. G., Cosgrove, R., Hine, C. H., McCauley, W. J., Stokey, E., Versey, R. E., Yuda, N. N., and SubbaRow, Y.: The pharmacology of duomycin, Ann. N. Y. Acad. Sci., 51:182 (Nov.), 1948.

25. Heilman, F. R.: Aureomycin in the treatment of experimental relapsing fever and leptospirosis icterohemorrhagica (Weil's Disease), Proc. Staff Meet. Mayo Clinic, 23:569 (Dec. 8), 1948.

26. Benedict, R. G., and Stodola, F. G.: Modification of an agar diffusion method of assay for polymyxin, J. Bact., 55:286 (Feb.), 1948.

27. Lennette, E. F., Meiklejohn, J., and Thelen, H. M.: The treatment of Q fever in man with aureomycin, N. Y. Acad. Sci., 51:331 (Nov.), 1948.

28. Little, P. A.: Use of aureomycin in some experimental infections in animals, Ibid., 246.

29. O'Leary, P. A., Keirland, R. R., and Herrell, W. E.: The oral administration of aureomycin (duomycin) and its effect on Treponema pallidum in man, Proc. Staff Meet. Mayo Clinic, 23:579 (Dec. 8), 1948.

30. Paine, Jr., T. F., Collins, H. S., and Finland, M.: Laboratory studies with aureomycin, Ann. N. Y. Acad. Sci., 51:228 (Nov.), 1948.

31. Paine, Jr., T. F., Collins, H. S., and Finland, M.: Bacteriologic studies on aureomycin, J. Bact., 56:489 (Oct.), 1948.

32. Payne, E. H., Knaudt, J. G., and Palacios, S.: Treatment of epidemic typhus with chloromycetin, J. Trop. Med. and Hyg., 51:68 (Jan.), 1948.

33. Pincoffs, M. C., Guy, E. L., Lister, L. M., Woodward, T. E., and Smadel, J. E., The treatment of Rocky Mountain spotted fever with chloromycetin, Ann. Int. Med., 29:656 (Oct.), 1948.

34. Price, C. W., Randall, W. A., and Welch, H.: Bacteriological studies of aureomycin, Ann. N. Y. Acad. Sci., 51:211 (Nov.), 1948.

35. Ross, S., Schoenbach, E. B., Burke, F. G., Bryer, M. S., Rice, E. C., and Washington, J. A.: Aureomycin therapy of Rocky Mountain spotted fever, J.A.M.A., 138:1213 (Dec. 25), 1948.

36. Schoenbach, E. B., Bryer, M. S., Bliss, E. A., and Long, P. H.: Polymyxin, a note on experimental and clinical investigations, J.A.M.A., 136:1096 (April 24), 1948.

37. Schoenbach, E. B., Bliss, E. A., and Chandler, C. A.: Treatment of experimental infections with aureomycin, Ann. N. Y. Acad. Sci., 51:254 (Nov.), 1948.

38. Schoenbach, E. B., Bryer, M. S., and Long, P. H.: The pharmacology and clinical trial of aureomycin; a preliminary report, Ibid., 267.

39. Schoenbach, E. B., and Bryer, M. S.: The treatment of primary atypical non-bacterial pneumonia with aureomycin, J.A.M.A., in press.

40. Smadel, J. E., and Jackson, E. B.: Chloromycetin, an antibiotic with chemotherapeutic activity in experimental rickettsial and viral infections, Science, 106:418 (Oct. 31), 1947.

41. Smadel, J. E., and Jackson, E. B.: Effect of chloromycetin on experimental infection with psittacosis and lymphogranuloma venereum viruses, Proc. Soc. Exp. Biol. and Med., 67:478 (April), 1948.

42. Smadel, J. E., Leon, H. E., Ley, H. L., and Varela, G.: Chloromycetin in the treatment of patients with typhus fever, Proc. Soc. Exper. Biol. and Med., in press.

43. Smadel, J. E., Woodward, T. E., Ley, Jr., H. L., Philip, C. B., Traub, R. B., Lewthwaite, R., and Savoor, S. R.: Chloromycetin in the treatment of scrub typhus, Science, 108:160 (Aug. 18), 1948.

44. Smith, R. B., Joslyn, D. A., Gruhzit, O. M., McLean, Jr., I. W., Penner, M. A., and Ehrlich, J.: Chloromycetin: biological studies, J. Bact., 55:425 (March), 1948.

45. Spink, W. W., Braude, A. I., Castaneda, M. R., and Goytia, R. S.: Aureomycin therapy in human brucellosis, J.A.M.A., 138:1145 (Dec. 18), 1948.

46. Stansly, P. G., Shepherd, R. D., and White, H. J.: Polymyxin, a new chemotherapeutic agent, Bull. Johns Hopkins Hosp., 81:43 (July), 1947.

47. Stansly, P. G., and Schlosser, M. E.: Studies on polymyxin: isolation and identification of bacillus polymyxa and differentiation of polymyxin from certain known antibiotics: an agar diffusion method of assay, J. Bact., 54:549 and 585 (Nov.), 1947.

48. Swift, N. P.: Treatment of pertussis with aerosporin, Lancet, I:133 (Jan. 24), 1948.

49. Wong, S. C., and Cox, H. R.: Action of aureomycin against experimental rickettsial and viral infections, Ann. N. Y. Acad. Sci., 51:290 (Nov.), 1948.

50. Woodward, T. E., Smadel, J. E., Ley, Jr., H. L., Green, R., and Manikas, D. S.: Preliminary report on the beneficial effect of chloromycetin in the treatment of typhoid fever, Ann. Int. Med., 29:139 (July), 1948.

51. Wright, L. T., Sanders, M., Logan, M. A., Prigot, A., and Hill, L. M.: Aureomycin, J.A.M.A., 138:408 (Oct. 9), 1948.

52. Wright, L. T., Sanders, M., Logan, M. A., Prigot, A., and Hill, L. M.: The treatment of lymphogranuloma venereum and granuloma inguinale in humans with aureomycin, Ann. N. Y. Acad. Sci., 51:318 (Nov.), 1948.

53. Youmans, G. P., Youmans, A. S., and Osborne, R. R.: Tuberculostatic action of chloromycetin *in vitro* and *in vivo*, Proc. Soc. Exper. Biol. and Med., 67:426 (April), 1948.