TABLE II. Fungicidal Activity of Polymyxins and Various Known Agents.

Agent	Minimum fungicidal concentration in mg %: *C. albicans* S*	*C. albicans* NS†	*T. mentagrophytes* S	*T. mentagrophytes* NS	*T. purpureum* S	*T. purpureum* NS	*M. audouini* S	*M. audouini* NS	*M. lanosum* NS
Polymyxin A	>25	>25	>25	25					
B	25	25	25	25					25
D	>25	>25	>25	>25					
E	25	25	25	25	25	25	12.5	25	
Benzoic acid	>25	>25	>25	>25	>25	25	25	12.5	25
Salicylic acid	>25	>25	>25	>25	>25	25	>25	25	25
Undecylenic acid	>25	25	12.5	6.25	>25	6.25	12.5	3.12	3.12
Asterol	>25	>25	12.5	>25	3.12	>25	6.25	25	>25
G-4	25	3.12	6.25	.78	6.25	.78	6.25	.39	.78

* Medium plus serum. † Plain medium.

it would appear unlikely that overgrowth of such types would be encountered during systemic use of these antibiotics. However, there would be the possibility that an increase in Gram-positive flora might result.

Summary. (1) Polymyxins A, B, D and E were tested for antifungal activity against 5 species of dermatophytes and 1 systemic fungus. Varieties B and E were the most active and of equal effectiveness. (2) Activity of the polymyxins was not significantly inhibited by serum. (3) Clinical trial of the topical and systemic efficacy of polymyxins B or E in mycotic infections is suggested.

1. Brownlee, G., Bushby, S. R. M., and Short, E. I., *Ann. New York Acad. Sci.*, 1949, v51, 952.

2. Bliss, E. A., and Todd, H. P., *J. Bact.*, 1949, v58, 61.

3. Frank, P. F., Wilcox, C., and Finland, M., *J. Lab. and Clin. Med.*, 1950, v35, 205.

4. Catch, J. R., Jones, T. S. C., and Wilkinson, S., *Biochem. J.*, 1948, v43, xxvii.

5. Catch, J. R., Jones, T. S. C., and Wilkinson, S., *Ann. New York Acad. Sci.*, 1949, v51, 917.

6. Rothman, S., Smiljanic, A. M., and Shapiro, A. L., PROC. SOC. EXP. BIOL. AND MED., 1945, v60, 394.

7. Rothman, S., Smiljanic, A. M., and Weitkamp, A. W., *Science*, 1946, v104, 201.

8. Serri, F., *Compt. rend. Soc. de biol.*, 1949, v143, 362.

9. Burlingame, E. H., and Reddish, G. F., *J. Lab. and Clin. Med.*, 1939, v24, 765.

10. Grunberg, E., Soo-hoo, G., Titsworth, E., Ressetar, D., and Schnitzer, R. J., *Trans. New York Acad. Sci.*, 1950, v13, 22.

11. Pulaski, E. J., Baker, H. J., Rosenberg, M. L., and Connell, J. F., Jr., *J. Clin. Invest.*, 1949, v28, 1028.

12. Jawetz, E., and Coleman, V. R., *J. Lab. and Clin. Med.*, 1949, v34, 751.

13. Hayes, E. R., and Yow, E., *Am. J. Med. Sci.*, 1950, v220, 633.

14. Kagan, B. M., Krevsky, D., Milzer, A., and Locke, M., *J. Lab. and Clin. Med.*, 1951, v37, 402.

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Terramycin Hydrochloride Alone and with Mapharsen and Bismuth in Treatment of Experimental Syphilis of Rabbits. (19301)

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As shown by Hobby and her associates(1), terramycin hydrochloride is absorbed readily from the gastrointestinal tract of rabbits with high concentrations in the blood within an hour following the oral administration of the compound. Under the circumstances we have thought it advisable to determine the therapeutic activity of terramycin hydrochloride alone and in combination with Mapharsen and bismuth salicylate in the treatment of acute

syphilitic orchitis of rabbits although Hendricks and his colleagues(2), and Schoch and Alexander(3) have found the compound by oral administration therapeutically effective in the treatment of early syphilis of human beings.

Methods and materials. Rabbits were inoculated intratesticularly with the Nichols-Hough strain of *T. pallidum* and treatment instituted 4 to 5 weeks later in animals developing acute orchitis with positive darkfield examinations. Following the institution of treatment, clinical and darkfield examinations were made daily for 3 days in succession and thereafter at weekly intervals over a period of 70 days at which time lymph nodes were inoculated intratesticularly in rabbits. These animals were kept under observation with repeated darkfield examinations, for a period of 8 weeks when the results were evaluated. Terramycin hydrochloride* was administered orally in sterile 5% solutions of acacia. Also by intramuscular injection in the same vehicle. Suspensions in sterile peanut oil could not be administered because of gelling. Rabbits with acute syphilitic orchitis were also treated with terramycin hydrochloride by oral and intramuscular administration along with Mapharsen (oxophenarsine hydrochloride) by intravenous injection and bismuth salicylate in oil with Chloretone (Parke, Davis & Co.) by intramuscular injection, for possible synergistic or additive chemotherapeutic activity. Two rabbits were treated with the same dose or doses in all treatment schedules.

Results. Oral administration. Single doses of 50, 75, and 100 mg per kg of weight of terramycin hydrochloride were without demonstrable treponemicidal activity. Single doses of 150, 200, and 250 mg per kg showed temporary treponemicidal effects but were not completely curative since the results of lymph node transfers were positive in all animals. Much better results, however, were observed when the compound was administered orally twice daily in doses of 2.5, 5, 10, and 15 mg per kg of weight for 15 days in succession. In these experiments the total minimal curative dose with negative lymph node transfers was approximately 150 to 300 mg per kg of weight. The single doses were well borne with no evidences of toxicity. The same was true of rabbits given 2.5 and 5 mg per kg twice daily over a period of 15 days. Doses of 10 and 15 mg per kg twice daily for 15 days in succession, however, produced anorexia with progressive loss of weight. Thus one of 2 rabbits given 15 mg twice daily for 15 days (totalling 450 mg) died on the 40th day while each of 2 rabbits given 20 mg twice daily for 15 days (totalling 600 mg) died 4 days after the cessation of treatment.

Intramuscular administration. Much better treponemicidal effects were observed when terramycin hydrochloride was given by intramuscular injection in single doses of 25, 50, 75, 100, 150, and 200 mg per kg of weight. Single doses of 25 and 50 mg produced temporary negative darkfield examinations but were not completely curative since positive lymph node transfers were observed. According to our results the single minimal curative dose by this route of administration was approximately 75 to 100 mg per kg of weight. When administered once a day in dose of 2.5, 5, 10, and 25 mg per kg of weight for 15 days in succession, the total minimal curative dose was approximately 75 to 100 mg per kg of weight. All rabbits given single intramuscular doses of 25 to 200 mg per kg of weight survived with no evidences of general toxic effects. The same was true of all rabbits given 2.5 to 25 mg per kg once daily for 15 days in succession, totalling 37.5 to 375 mg per kg of weight. On the other hand, however, inflammatory reactions were generally observed at the sites of injection which progressed to necrosis in some animals given the larger doses.

Terramycin hydrochloride in combination with Mapharsen and bismuth. The oral administration of 2.5 mg terramycin hydrochloride per kg of weight twice daily for 15 days in succession (totalling 75 mg) was without detectable therapeutic activity. However, when given along with Mapharsen by intravenous injection in dose of 0.3 mg per kg every 3 days for 5 doses (totalling 1.5 mg), this dose of terramycin hydrochloride was

* Kindly supplied by Chas. Pfizer and Co., through the courtesy of Dr. Ray A. Patelski.

completely curative with negative lymph node transfers. The same results were observed when 0.5 mg bismuth salicylate per kg of weight was given every 3 days for 5 doses (totalling 2.5 mg) by intramuscular injection. Similar results were observed with terramycin hydrochloride administered intramuscularly. Thus the administration of 2.5 mg per kg once daily for 15 doses (totalling 37.5 mg) was without detectable therapeutic activity. But when administered along with 0.3 mg Mapharsen per kg by intravenous injection every 3 days for 5 doses (totalling 1.5 mg), this dosage of terramycin hydrochloride was completely curative with negative lymph node transfers. The same results were observed when bismuth salicylate was administered intramuscularly every 3 days for 5 injections in dose of 0.5 mg per kg (totalling 2.5 mg). Since both Mapharsen and bismuth salicylate alone in these doses per kg of weight were not completely curative with positive lymph node transfers, it is apparent that both compounds act synergistically or additively with terramycin hydrochloride in the treatment of experimental syphilis of rabbits, as has been observed with penicillin(4-6).

Summary. (1) Terramycin hydrochloride by oral administration in single doses of 50 to 250 mg per kg of weight were not completely curative in the treatment of acute syphilitic orchitis of rabbits. (2) When administered orally twice daily for 15 days in succession the total minimal curative dose was 150 to 300 mg per kg of weight. (3) By intramuscular injection the single minimal curative dose was 75 to 100 mg per kg of weight. When administered once daily for 15 days in succession the total minimal curative dose was 75 to 150 mg per kg by this route of administration. (4) Mapharsen by intravenous injection and bismuth salicylate by intramuscular injection yielded pronounced synergistic or additive therapeutic effects when given along with terramycin hydrochloride by oral and intramuscular administration.

1. Hobby, G. L., Reed, W., Rinnie, D., Powers, M., and D'Ambrosia, A., PROC. SOC. EXP. BIOL. AND MED., 1950, v73, 511.

2. Hendricks, F. D., Greaves, A. B., Olansky, S., Taggart, S. R., Lewis, C. N., Landman, G. S., MacDonald, G. R., and Welch, H., *J.A.M.A.*, 1950, v143, 4.

3. Schoch, A. G., and Alexander, L. J., *Ann. N. Y. Acad. Sci.*, 1950, v53, 459.

4. Kolmer, J. A., and Rule, A. M., *Arch. Dermat. and Syph.*, 1947, v56, 179.

5. ———, *Arch. Dermat. and Syph.*, 1948, v57, 965.

6. ———, *Am. J. Syph., Gonorr. and Ven. Dis.*, 1950, v34, 45.

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Hibernation in the Alligator. (19302)

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In common with several other species of reptiles the reaction of the alligator to various types of stimuli is slow enough to allow the observer much more time than would be the case if warm blooded animals had been employed(1,2). Unfortunately the concentration of various blood constituents is not constant but is subject to certain seasonal changes. McIlhenny(3) commented on the fact that the alligator does not eat for several months in the winter either in his native habitat or in the confines of a heated zoological garden. This loss of the desire to eat constituted almost the sole experimental evidence that the alligator is an animal which hibernates in the winter. In the course of over 3 years of research we have been able to collect a considerable amount of data on the effect of season on the alligator and on the caiman, a closely related tropical species.

Effect of temperature and light on blood glucose and growth rate. About 200 alligators and 35 South American caimans were observed under laboratory conditions. Pre-