TABLE II. Complement-Fixation Titers of Sera with Measles Agent Tissue Fluid Antigens.

Titer range*	Sera from cases of measles: Days after onset† <5	Sera from cases of measles: Days after onset† >5	Heterologous sera
<4	7	0	7
5- 25	1	1	11
26- 50	0	1	5
51-100		3	2
101-200	1		1
>200		4‡	

* Titers = Number of 50% units of complement fixed.

† Exact date of onset unknown in some cases; may refer to earliest symptoms or appearance of rash.

‡ Three additional sera from one patient taken 3 to 4½ months after onset fell in this group.

direct fluorescein-labeled antibody technic before specific complement-fixation antigen appeared in the fluid phase. Specific fluorescence due to the presence of measles antigen was noted in the nuclei as well as in the cytoplasm of some cells from infected cultures.

1. Enders, J. F., and Peebles, T. C., PROC. SOC. EXP. BIOL. AND MED., 1954, v86, 277.

2. Coons, A. H., and Kaplan, M. H., *J. Exp. Med.*, 1950, v91, 1.

3. Weller, T. H., and Coons, A. H., PROC. SOC. EXP. BIOL. AND MED., 1954, v86, 789.

4. Tompkins, V., and Macaulay, J. C., *J.A.M.A.*, 1955, v157, 711.

5. Youngner, J. S., PROC. SOC. EXP. BIOL. AND MED., 1954, v85, 202.

6. Hazen, E. B., and Brown, R., *ibid.*, 1951, v76, 93.

7. Wadsworth, A. B., *Standard Methods of the Division of Laboratories and Research of the New York State Department of Health*, 3rd ed., Williams and Wilkins, Baltimore, Md., 1947, p. 226.

8. Buckley, S. M., Whitney, E., and Rapp, F., PROC. SOC. EXP. BIOL. AND MED., in press.

9. Healy, G. M., Fisher, D. C., and Parker, R. C., *Canad. J. Biochem. and Physiol.*, 1954, v32, 327.

10. Rustigian, R., Johnston, P., and Reihart, H., PROC. SOC. EXP. BIOL. AND MED., 1955, v88, 8.

11. Enders, J. F., personal communication, August 30, 1955.

12. Leduc, E. H., Coons, A. H., and Connolly, J. M., *J. Exp. Med.*, 1955, v102, 61.

13. Buckley, S. M., *Arch. ges. Virusforsch.*, in press.

Received September 1, 1955. P.S.E.B.M., 1955, v90.

Chemotherapy of Experimental Schistosomiasis. IV. Oral Activity of Antimony Trichloride Antibiotic Complexes. (21958)

GEORGE W. LUTTERMOSER, HOWARD W. BOND, AND JOHN F. SHERMAN.
(Introduced by Nathan B. Eddy.)

From the U. S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, National Microbiological Institute, Laboratory of Tropical Diseases, Bethesda, Md.

1 - (Diethylaminoethylamino) - 4 - methylthiaxanthone, Miracil D, was the first non-antimonial compound found to be of value for the oral treatment of schistosomiasis(1). In later studies, however, Miracil D proved to be toxic to man at therapeutic dosage levels(2,3). Other compounds which have been used with varying degrees of success in the oral treatment of schistosomiasis in man or experimental animals include antimony potassium tartrate, tartar emetic(4); sodium antimony III bis-pyrocatechol-2,4-disulfonate, Fuadin (5); various thioantimonials(6); and some symmetrical diaminodiphenoxyalkanes(7). During the course of screening compounds in this laboratory, it was found that the antimony trichloride complexes of oxytetracycline, Terramycin; of chlortetracycline, Aureomycin; and of tetracycline were schistosomacidal in white mice. The present report includes a comparison of the oral activities of these complexes and of other antimony compounds.

Materials and methods. Samples of the 3 complexes were synthesized by Dr. Philip N. Gordon and were submitted for evaluation by Chas. Pfizer & Co., Inc. The dithiastibiole compound mentioned below was supplied

TABLE I. Toxicity and Activity of Antimony Compounds.

Compound	Acute oral LD_{50}		Treatment results	
	Drug (mg/kg)	Sb equivalent (mg/kg)	No. mice	% reduction of worms by 10 oral doses totaling 350 mg Sb/kg
Terramycin antimony trichloride	1450	174	35	53.5
Aureomycin antimony trichloride	1550	248	35	83.6
Tetracycline antimony trichloride	1110	187	24	91.0
Fuadin	>1200	>162	15	0
Tartar emetic	540	198	18	94.3
Antimony trichloride	510	272	14	81.2
4,5-Dihydro-2-hydroxy-4-methylol-1,3,2-dithiastibiole	>1575	>732	9	0

through the courtesy of Abbott Laboratories. The drugs were given orally to white Swiss mice. In addition, the complexes were tested by the subcutaneous and intraperitoneal routes. After the compounds were found to be schistosomacidal by the preliminary method of screening described by Luttermoser(8), further evaluation of their activities was carried out as follows. Commencing on the 35th day after exposure to about 300 *Schistosoma mansoni* cercariae, mice in groups of 5 or 6 each were treated orally twice daily with the same dose of antimony in the form of one of the different compounds for a period of 5 days. Two to 3 weeks after treatment, the animals were killed and the schistosomes living in the portal system were perfused out by the technic of Yolles *et al.*(9) and counted. Small pieces (1 cm^2) of the livers of the treated mice were pressed between glass slides and examined for dead worms trapped in lesions. Unless dead worms were found, no reduction in worm infection was claimed. The worms living in the untreated mice were likewise isolated and counted by the same procedure. The percentage of worms remaining alive in the treated groups was inferred from the total number of living worms recovered from the treated mice relative to the number obtained from the untreated mice. From these data the percentage reduction in infection resulting from treatment was calculated. The LD_{50} values were determined on mice by the method of Litchfield and Wilcoxon(10).

Results. Table I summarizes the data on the activity and toxicity of the various compounds. The minimum oral dose of the Terramycin antimony trichloride complex which cleared the mice of more than one-half of their parasites was about 300 mg/kg (equivalent to about 35 mg antimony/kg) of body weight, while the oral LD_{50} of this compound for uninfected mice was about 1450 mg/kg(11). Fuadin, one of the drugs of reference, was not schistosomacidal at oral doses as high as 425 mg/kg. The curative results obtained with the first complex given orally at a level equivalent to 35 mg antimony/kg twice daily for 5 days were compared with those obtained by giving the same oral dose of antimony in the form of tartar emetic, antimony trichloride, and 4,5-dihydro-2-hydroxy-4-methylol-1, 3, 2-dithiastibiole. The Terramycin complex was more active than the last-named compound, which was reported by Schubert(6) to be among the most active schistosomacidal compounds when fed to mice at higher levels than used in this study. In comparison with tartar emetic and with antimony trichloride, the Terramycin antimony complex demonstrated no advantage in activity at this dosage. When Terramycin and antimony trichloride in quantities equivalent to the dosage of the complex were given separately but one following the other, reduction of live parasites equal to that obtained by administration of the Terramycin antimony complex was observed. Oral regimens of Terramycin, Aureomycin, or tetracycline alone were not schistosomacidal at oral doses comparable to the amount of these antibiotics in the complexes. Preliminary comparison of the activities and toxicities of the Terramycin antimony complex with the Aureomycin and tetracycline complexes (Table I) indicates that the last 2 are more active than the first but have similar toxicities.

Thus the apparent therapeutic advantage of the Aureomycin antimony complex or the tetracycline antimony complex over the Terramycin antimony complex is questionable. The 3 antibiotic antimony complexes were active following subcutaneous or intraperitoneal injection, but were toxic at doses of 50 mg/kg and higher.

Discussion. It appears probable that the schistosomacidal activity and toxicity of the 3 antibiotic complexes result almost entirely from their antimony content, and that variations in the efficacy of these compounds compared with the other antimony-containing preparations mentioned arise from differences in solubility, absorption, and dissociation. Such variations in activity further emphasize the need for additional investigation of organic antimonial compounds which are schistosomacidal upon oral administration.

Summary. The antimony trichloride complexes of Terramycin, Aureomycin, and tetracycline were active orally against *S. mansoni* infections in white Swiss mice. These compounds were no more active than tartar emetic or antimony trichloride.

1. Kikuth, W., Gonnert, R., and Mauss, H., *Naturwiss.*, 1946, v33, 253.

2. Halawani, A., *J. Roy. Egyptian M. A.*, 1949, v32, 29.

3. da Silva, J. R., *Rev. brasil. med.*, 1953, v9, 577.

4. Walker, J., *Ann. Soc. belge de méd. trop.*, 1928, v8, 273.

5. El Ayadi, S. M., *J. Roy. Egyptian M. A.*, 1947, v30, 562.

6. Schubert, M., *Am. J. Trop. Med.*, 1948, v30, 525.

7. Raison, C. G., and Standen, O. D., *Brit. J. Pharmacol.*, 1955, v10, 191.

8. Luttermoser, G. W., *J. Parasitol.*, 1954, v40, 130.

9. Yolles, T. K., Moore, D. V., DeGiusti, D. L., Ripsom, C. A., and Meleney, H. E., *ibid.*, 1947, v33, 419.

10. Litchfield, J. T., Jr., and Wilcoxon, F., *J. Pharmacol. and Exp. Therap.*, 1949, v96, 99.

11. Personal communication from Dr. J. E. Lynch, Pfizer Therapeutic Institute.

Received September 7, 1955. P.S.E.B.M., 1955, v90.

Effect of Liver Damage and Nephrectomy on Convulsant Potency of Pentylenetetrazol (Metrazol)* (21959)

DONALD O. SCHIFFMAN, EWART A. SWINYARD, AND LOUIS S. GOODMAN.

From the Departments of Pharmacology, University of Utah College of Pharmacy and College of Medicine, Salt Lake City.

There is lack of agreement on the fate and excretion of pentylenetetrazol (Metrazol) in laboratory animals and man. On the basis of data obtained by *chemical procedures,* Tatum and Kozelka(1) concluded that Metrazol is detoxified by the liver in dogs and man, whereas Esser and Kuehn(2) reported that the major portion of the drug is excreted by the kidney in man. Recent studies in our laboratory(3) with radioactive Metrazol indicate that most of a given dose of the drug in rats is excreted by the kidney in an altered form. On the basis of data obtained by *biological procedures,* Dille and Seeberg(4) concluded that Metrazol is degraded by the liver in cats, whereas Voss(5) reported that the drug is largely excreted by the kidney in rats. In view of these conflicting reports, it was thought important to make a systematic study of the effect of liver damage and of nephrectomy on the convulsant activity of this agent. It was anticipated that such a study would contribute information on the relative role of the liver and the kidney in the detoxification and excretion of Metrazol. The results obtained provide the basis for this report.

Methods. Adult male albino mice obtained from the Carworth Farms (CF #1) and adult male albino rats obtained from the Holtzman-Rolfsmeyer Farms were used as experimental

* This investigation was supported by a grant from the National Institute of Neurological Diseases and Blindness, National Institutes of Health, Public Health Service.