PAH than of creatinine in cortex. Consequently, if creatinine were secreted as has been proposed(2,3) its accumulation in the cells should be minimal compared to the intracellular accumulation of PAH.

One of the physiological implications from the study of renal tissue concentrations in free-flow and stop-flow kidneys is the localization of a secretory process in a region of the kidney. It was found that localization could be accomplished in osmotic diuresis but not in oliguria(1). From present experiments one may conclude that osmotic diuresis must be induced by injection of substances that are poorly reabsorbed (*i.e.*, mannitol, Na_2SO_4 or $Na_4Fe(CN)_6$) to localize a secretory process in obstructed kidneys, since under these conditions most of the secreted material remains at its site of secretion. In NaCl, $NaHCO_3$, of $NaNO_3$ diuresis the secretory process could not be localized due to the high degree of persistent movement of fluid along the nephron during the stop-flow period.

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Molluscan *Schistosomiasis mansoni*: Effect of 2 Analogues of Chloramphenicol on Both Parasite and Host.* (31853)

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The suppression of molluscan schistosomiasis with chloramphenicol, an antibiotic which inhibits protein synthesis, has recently been demonstrated(1,2). In the search for a cheaper and more active suppressant compound which might be of practical value in the control of schistosomiasis, further studies were initiated with two analogues of this drug: 1) the L-form of chloramphenicol, which is an almost bacteriologically inactive by-product of the production of the active D-form(3), and 2) the methyl-sulfonyl derivative of chloramphenicol, Thiocymetin®, which has been demonstrated to be of greater potency than its parent compound(4).

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Materials and methods. The toxicity of D- and L-chloramphenicol and Thiocymetin® was determined by dissolving different amounts of each drug in 2 L of dechlorinated water in stainless steel pans and adding twenty 10-12 mm *Australorbis glabratus* of a Puerto Rican strain to each container. Each experiment included a control group similarly maintained but without the addition of drug. At 72 hours all of the animals were placed in fresh dechlorinated water and the number of dead snails determined.

Experiments on the suppressive effect of the two drugs on molluscan schistosomiasis were then initiated by exposing large numbers of snails individually to 15-20 miracidia of a Puerto Rican strain of *Schistosoma mansoni*. Twenty-four hours later a control group of 20 snails, chosen at random, was placed in an aerated, covered stainless steel pan in 4 L of dechlorinated water maintained at 23° C and

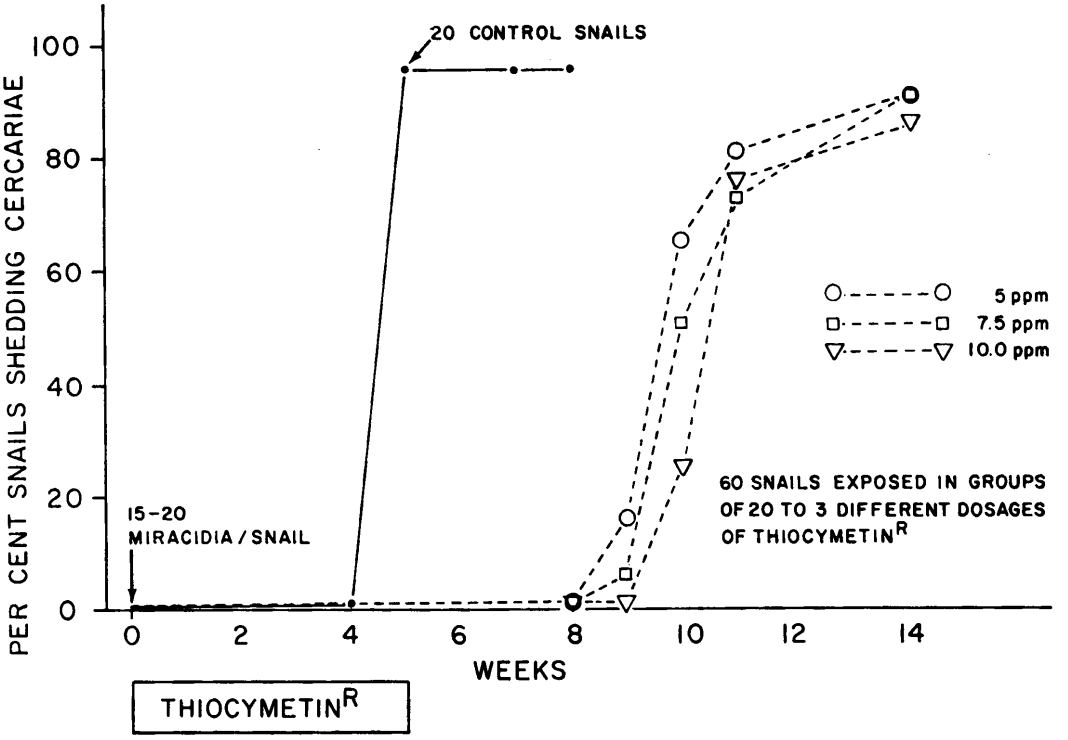

FIG. 1. Effect of 5 weeks of exposure to the methyl sulfonyl analogue of D-chloramphenicol (Thiocymetin®) on shedding of cercariae by snails previously exposed to miracidia of *S. mansoni*.

fed lettuce *ad libitum*. Groups of 20 experimental snails were similarly chosen and maintained with the addition of different amounts of the 2 drugs to the water. The drugs in the experimental groups, and the water in those and the control group, were changed weekly until the fifth week when the snails were transferred to water without drug. At the fifth week and weekly thereafter each snail was placed individually in 3 ml of dechlorinated water for 30 minutes in order to determine whether they were shedding cercariae.

Results. L-chloramphenicol was more toxic to the snails than D-chloramphenicol, the LD_{50} of the former being 1122 $\pm$ 13.6 μg/ml or parts per million (ppm) and the latter 1295 $\pm$ 11.0 ppm. Thiocymetin®, however, killed no snails in 72 hours at the maximal concentration that could be dissolved in water —between 7,500 and 10,000 ppm.

The effect of a given concentration of a drug on molluscan schistosomiasis was designated as complete suppression if the snails failed to produce cercariae for a period of time at least equal to their exposure to the compound, *e.g.*, control snails shed cercariae 5 weeks after exposure to miracidia, whereas snails exposed to a completely suppressant drug during this initial 5-week period began shedding at 10 weeks. The lowest concentration of D-chloramphenicol which completely suppressed molluscan schistosomiasis was 20 ppm. At that dosage L-chloramphenicol had no suppressive effect and even at 625 ppm it provided only minimal suppression, more than 50% of the snails shedding cercariae 8 weeks after exposure to miracidia. In contrast, Thiocymetin® completely suppressed the disease at 10 ppm (Fig. 1), half the concentration of D-chloramphenicol which provided similar suppression.

Since the therapeutic ratio of Thiocymetin® (completely suppressive dose/snail LD_{50}) was much greater than that of D-chloramphenicol (>750:1 as opposed to 60:1), further studies were undertaken with it. When snails were maintained in various

concentrations of the drug for prolonged periods, the drug being changed at 4-week intervals, the following occurred: Snails kept continuously at a concentration of 2.5 ppm shed at 6 weeks rather than at 5 weeks as had the controls. At 5.0 ppm 53% shed cercariae at the eleventh week. No shedding at all occurred in the snails maintained at 10 ppm for 16 weeks; they began to shed at 21 weeks, 5 weeks after they were removed to fresh water.

Studies of the effect of Thiocymetin® on the growth and egg-laying of snails were then performed. Four groups of 20 snails each (a control group and 3 groups exposed respectively to 312, 1500 and 3000 ppm of the drug) were maintained as described above. There were no deaths during the 4 weeks of exposure attributable to even the highest concentration of the drug. Although Thiocymetin® at 312 ppm provided some degree of inhibition of both growth and egg-laying it was not as effective as D-chloramphenicol. The latter drug at a concentration of 625 ppm provided virtually complete inhibition of snail growth and egg-laying. In order to achieve a similar result on growth and egg-laying with Thiocymetin® a concentration of 3000 ppm was necessary.

Discussion. The two analogues of D-chloramphenicol tested in the present experiment gave interestingly opposite results from those of the parent compound. L-chloramphenicol was significantly more toxic than the D isomer, but had no effect on molluscan schistosomiasis. In contrast, the methyl-sulfonyl analogue of D-chloramphenicol, Thiocymetin®, was non-lethal to snails and had less effect on snail growth and egg-laying, but was twice as effective in suppressing the disease.

In relation to the mechanism of action of these drugs a recent study of the biochemical effects of D- and L-chloramphenicol should be mentioned(5). Whereas D-chloramphenicol at low concentrations will block protein synthesis in many systems, at higher concentrations it may impair oxidative phosphorylation. L-chloramphenicol which has virtually no effect on protein synthesis is a somewhat more effective inhibitor of oxidative phosphorylation than its isomer. On the basis of these results it was stated that when only the D-isomer is effective on tissue, there is reason to believe that protein synthesis is the process being inhibited; when both the D and L compounds are effective, impairment of phosphorylation is involved(5). It is intriguing to think, therefore, that the toxic effects of both D- and L-chloramphenicol on the host snail are due to an impairment of one biochemical mechanism, oxidative phosphorylation, whereas the effect of D- chloramphenicol alone (at much lower concentrations) on the parasitic schistosome is due to an entirely different mechanism, inhibition of protein synthesis. Furthermore, studies on Thiocymetin® might reveal that it has relatively little ability to impair oxidative phosphorylation.

Summary. Following the observation that D-chloramphenicol suppresses molluscan schistosomiasis, 2 analogues of this compound were studied. L-chloramphenicol was somewhat more lethal to snails than D-chloramphenicol but had little effect on the disease. In contrast, the methyl-sulfonyl analogue of D-chloramphenicol was non-lethal to snails and was twice as effective against the disease as the parent compound.

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