subcutaneously with 0.5 ml of saline containing the antibiotic[3] in the doses indicated in Table 1. Control mice received daily injections of 0.5 ml saline subcutaneously for the same period of time.

TABLE 1

EFFECT OF ANTIBIOTIC THERAPY ON THE MORTALITY OF MICE EXPOSED TO 450 R X-RADIATION

Drug	Dose	Animals irradiated	% Dead at 30 days
Streptomycin	6,000 μg	128*	16
Controls†	.....	127*	81
Streptomycin	5,000 μg	101*	34
Controls†	.....	101*	89
Streptomycin	7,000 μg	88‡	30
Controls†	.....	88‡	77
Penicillin	10,000 units		
Streptomycin plus ...	5,000 μg	72‡	25
Controls†	.....	72‡	66
Chloramphenicol	2.0 mg	47‡	36
Controls†	.....	45‡	60

* Total in 3 experiments.

† Control mice were injected subcutaneously with 0.5 ml saline daily for the same period—24 days.

‡ Total in 2 experiments.

Results. The results, presented in Table 1, show that streptomycin administered subcutaneously once a day from the 4th through the 28th day after irradiation significantly reduced the mortality during the 30-day period of observation. In the group treated with 6,000 μg of streptomycin, 16% died, as compared with 81% of the controls. Doses of 5,000 and 7,000 μg of streptomycin showed less striking but still significant degrees of protection.

The group treated with a combination of 5,000 μg of streptomycin and 10,000 units of penicillin had a 30-day mortality of 25% compared with 66% for the controls.

Preliminary trials with other antibiotics have shown chloramphenicol (chloromycetin) to be somewhat less effective than streptomycin alone or in combination with penicillin. Chloramphenicol, as well as aureomycin, caused a considerable degree of irritation at the site of the injection. In some of the mice there was even necrosis of the skin. These deleterious effects are being obviated in current experiments in which the drug is administered in food.

Polymyxin B in doses of 0.2, 0.1, 0.05, and 0.02 mg failed to reduce the mortality. In fact, the death rate was increased by the larger dose, presumably because of its toxicity.

Results with aureomycin were irregular. One experiment showed a significant reduction in mortality but another experiment showed none, probably because infection with a strain of *Pseudomonas aeruginosa* insensitive to aureomycin appeared among the mice in that group.

[3] The streptomycin and polymyxin were provided by Chas. Pfizer & Co.; the penicillin by Commercial Solvents Corporation, Eli Lilly & Co., and Schenley & Co.; the aureomycin by Lederle & Co.; the chloromycetin by Parke-Davis & Co.

It seems evident, therefore, that, to be effective in reducing mortality from irradiation injury in mice, a chemotherapeutic agent must provide protection against infections by bacteria normally present in the animal, and also against all pathogens which might establish themselves within its body during the period when the animal's natural resistance to infection is markedly reduced. Among the antibiotics tested, streptomycin has provided the most effective protection.

Reference

1. MILLER, C. PHILLIP, HAMMOND, CAROLYN W., and TOMPKINS, MARIANNE. *Science*, 1950, **111**, 540.

New Chemotherapeutic Agents in Enterohepatitis (Blackhead) of Turkeys

E. Waletzky, J. H. Clark, and H. W. Marson[1]

Chemotherapy Division, American Cyanamid Company, Stamford, Connecticut

The need for an economical chemotherapeutic agent for the treatment or prevention of enterohepatitis (blackhead) of the turkey and chicken encouraged the trial in enterohepatitis of compounds with suppressive activity in other protozoan infections. It seemed desirable to test a large variety of such agents in view of the wide taxonomic gap between *Histomonas meleagridis* and other pathogenic protozoa, and the generally limited correlation between activity in different protozoan infections, e.g., malaria and coccidiosis (*4*). Twenty-four compounds of 17 different structural types active in experimental cecal coccidiosis (*Eimeria tenella*) of the chicken, mainly at somewhat toxic or at uneconomically high concentrations (*5*), and six types of antimalarials were tested in young infected turkeys by the drug-diet method. Standardized enterohepatitis infections were obtained by the rectal inoculation of homogenates from livers with freshly formed lesions.

A high degree of suppressive activity in enterohepatitis at nontoxic diet concentrations was shown only by 2-amino-5-nitropyrimidine (*3*) (Enheptin-P),[2] a compound with a moderate degree of anticoccidial activity at slightly toxic concentrations in the chicken (0.15%). On the other hand, such highly active anticoccidials as the sulfanilamide derivatives or nitrophenide, and such antimalarials as chloroquine or chlorguanide, as well as the 18 other types of compounds tested, were inactive. 2-Amino-5-nitropyrimidine almost completely prevented mortality (12%) and the development of cecal and liver lesions in 164 birds when 0.1% concentrations of drug in the diet were given for 7 to 14 days and when treatment was begun not later than 3 days after rectal inoculation. The 215 untreated controls in these 13 tests suffered 80%

[1] The assistance of C. O. Hughes in the early phase of the biological work, and of M. C. Brandt, A. Bliznick, and S. Brackett in its later phase, is gratefully acknowledged.

[2] Enheptin-P is a trademarked product.

mortality at an average of 11 to 12 days after inoculation. Drug concentrations as low as 0.0375% in the diet for 14 days after inoculation prolonged survival time considerably. Enheptin-P was also highly active in enterohepatitis produced by the oral inoculation of *Heterakis gallinae* ova, which is the presumptive major mode of naturally occurring infections.

Accordingly, a large number of related heterocycles were prepared (J. H. Clark and H. W. Marson) of which the most promising, 2-amino-5-nitrothiazole (*1*, *2*) (Enheptin-T)[3] may be equally active and can be produced

TABLE 1

THE EFFECT OF ENHEPTIN-T* (2-AMINO-5-NITROTHIAZOLE) ON ENTEROHEPATITIS OF TURKEYS PRODUCED WITH *Heterakis gallinae* OVA

Days treated†	% Drug in diet	No. alive/total‡		Days survival§	
		Treated	Control	Treated	Control
1–15 B	0.10	7/7	3/10	..	18
1–15 B	0.05	9/9	3/10	..	18
3–17 A	0.15	8/8	1/8	..	17
4–18 B	0.10	7/10	3/10	31	18
4–18 B	0.05	4/10	3/10	28	18
5–19 A	0.15	5/8	1/8	32	17
7–21 B	0.10	4/9	3/10	34	18
7–21 B	0.05	2/10‖	3/10	30	18
13–21# C	0.10	1/5**	2/10	25	14
13–21# and 21–28 B	0.15 and 0.05	6/10	3/10	41	18

* Enheptin-T is a trademarked product.

† Single oral inoculation with about 300 *Heterakis* ova at 0 days in tests A, B, and C.

‡ Seven weeks after inoculation in A, 8 weeks in B and C.

§ Average of dead birds only.

‖ Two deaths during treatment. All other deaths except ** after treatment stopped.

Treatment begun when clinical symptoms appeared in group.

** One death during treatment.

much more economically than Enheptin-P. In eight experiments with 96 rectally inoculated poults treated with 0.035% or 0.05% of Enheptin-T for 14 days, the average prolongation of survival time by 10 to 15 days was at least as great as that obtained with Enheptin-P. Although two weeks of treatment with 0.1% (81 birds) or 0.05% (116 birds) of the thiazole compound did not reduce delayed mortality (after treatment halted) as much as similar Enheptin-P treatments, this may only reflect the lower control mortality of the latter tests. In any event, 0.05% of Enheptin-T suppressed mortality completely during treatment, and for more than one week after treatment halted, in rectally inoculated birds treated for 4 weeks (15 birds), for 6 weeks (11 birds), for 8 weeks (15 birds), or for 12 weeks (14 birds). This indicates the efficacy of 0.05% for long term, continuous treatment. Such treatment, or repeated intermittent treatments, may prove necessary in the field with either of these drugs, since substantial, acquired immunity to severe experimental challenges was absent in drug-treated survivors of experimental infections. (However, our data do not exclude the possibility that such immunity may follow repeated exposure to infection, or may be adequate with the lighter challenges that probably occur in the field.)

Enheptin-T is highly active in enterohepatitis produced with *Heterakis* ova (Table 1). Complete prevention of mortality was obtained when 14 days of treatment was begun not later than 72 hr after a single oral inoculation. With treatments begun later, there was generally some reduction in mortality, and very few deaths occurred until more than one week after treatment stopped, even when treatment was not begun until the appearance of clinical symptoms (13 days). This suggests that longer treatments might have saved most of the birds. The activity of Enheptin-T, and of Enheptin-P, has been confirmed by others in naturally occurring field outbreaks and will be reported elsewhere, as will full details of the above results.

[3] Enheptin-T is a trademarked product.

References

1. GANAPATHI, K. and VENKATARAMAN, A. *Proc. Indian Acad. Sci.*, 1945, **22A**, 354.
2. ———. *Chem. Abstr.*, 1946, **40**, 4058.
3. HALE, W. J. and BRILL, H. C. *J. Amer. chem. Soc.*, 1912, **34**, 91.
4. WALETZKY, E. and HUGHES, C. O. *Amer. J. vet. Res.*, 1946, **7**, 365.
5. ———. Unpublished data.

Effect of Adrenalectomy on Liver Catalase Activity in the Rat[1]

R. W. Begg and E. F. Reynolds

Cancer Research Laboratory,
Department of Biochemistry,
Dalhousie University, Halifax, Canada

Adrenal cortical secretions have been shown to influence enzyme activity, both by removal of the adrenals and by injection of adrenal cortical extracts (*4*, *5*). It has been demonstrated that cytochrome oxidase is diminished in activity by adrenalectomy of the rat (*7*).

In connection with studies on liver catalase activity in normal and tumor-bearing rats, we needed to know whether adrenalectomy could alter liver catalase activity. Accordingly, Sprague-Dawley-Holtzman rats of both sexes were adrenalectomized by the lumbar approach under aseptic conditions. The animals were maintained postoperatively at a constant temperature on a diet high in sodium and low in potassium (*1*). Control rats were maintained in the same environment and on the same diet, but given tap water. The rats were sacrificed 14–21 days after adrenalectomy and liver catalase activity was determined by a titrimetric method (*2*).

The results are presented in Table 1, from which it is evident that adrenalectomy decreases liver catalase activity in the rat. Though a sex difference in liver catalase activity has been reported (*6*), it was not noted in

[1] Aided by grants from the Banting Research Foundation and the National Cancer Institute of Canada.