10. Eguchi, Y., Eguchi, K., Wells, L. J., Proc. Soc. Exp. Biol. and Med., 1964, v116, 89.
11. Jailer, J. W., ibid., 1949, v72, 638.
12. ———, Endocrinology, 1950, v46, 420.
13. Milkovic, K., Milkovic, S., Endocrinologie, 1959, v37, 301.
14. Schapiro, S., Geller, E., Eiduson, S., Proc. Soc. Exp. Biol. and Med., 1962, v109, 937.

Received September 9, 1965. P.S.E.B.M., 1965, v120.

Effect of Primidone (Mysoline) on Tissular Levels of Griseofulvin in the Rat. (30622)

M. KRAML, A. V. MARTON* AND D. DVORNIK (Introduced by C. Chappel)
(With the assistance of Luba Garbaczewska)
Department of Biochemistry, Ayerst Research Laboratories, Montreal, Canada

The antibiotic griseofulvin is a potent systemic agent in the treatment of superficial fungal infections in man(1). The effectiveness of griseofulvin appears to be related to its concentration in the blood, which, in turn, will depend mainly on the gastrointestinal absorption of griseofulvin(2) and on the rate of its metabolic degradation.

The finding of reduced blood-griseofulvin levels in rats(3) and humans(4) pretreated with phenobarbital may indicate enhanced rate of metabolism. In view of this possibility, we considered it interesting to investigate the structurally similar anticonvulsant agent 5-ethyl-5-phenylhexahydropyrimidine-4, 6-dione (primidone, Mysoline®) for its possible effect on griseofulvin content in rat blood and liver.

Methods. Ten female albino rats weighing about 150 g were used per group. The control group received saline. Over a period of 8 days the second group was given a daily oral dose of 20 mg/kg of phenobarbital sodium and the third group 20 mg/kg of primidone, respectively. On day 9 all animals received a single oral dose of 50 mg/kg of griseofulvin; so as to maximize gastrointestinal absorbtion(5), a fine-particle-state preparation (Grisactin®) was used. Since serum griseofulvin levels are highest 4 hours after oral dose(5), all animals were killed after 4 hours and the concentration of griseofulvin in the serum and liver was determined by a modification(6) of the fluorimetric method of Bedford, Child and Tomich(7). An Aminco-Bowman spectrophotofluorometer was used.

TABLE I. Effect of Primidone and of Phenobarbital on Levels of Griseofulvin in Rats.

Pretreatment (8 days)	Conc of griseofulvin* Serum, μg/100 ml	Liver, μg/g wet wt
Saline	4.77 ± .32†	17.9 ± .9
Primidone‡	2.89 ± .44 (−39%)	12.4 ± 1.4 (−31%)
Phenobarbital‡	2.96 ± .47 (−38%)	13.3 ± 1.3 (−26%)

* Four hours after 50 mg/kg griseofulvin *per os*. Average values of 2 experiments each with 10 rats per group.
† Standard error.
‡ Daily oral dose of 20 mg/kg.

Results. The average concentrations of griseofulvin in rat serum and livers as determined in 2 separate experiments are presented in Table I. Compared to untreated animals, repeated administration *per os* of Mysoline followed by a single oral dose of griseofulvin caused a statistically highly significant fall ($p<0.01$) of griseofulvin content in rat serum and livers. The degree of reduction was virtually identical with that detected in animals pretreated with phenobarbital which, in turn, are in agreement with those reported earlier(3).

Discussion. Recently, Conney and Burns (8) have reviewed the capacity of drugs to increase the activity of a wide variety of liver microsomal enzymes involved in drug metabolism. Among these is the enzyme system causing dealkylation of aromatic ethers. As such dealkylation appears to be an important reaction in the major pathway of griseo-

* Deceased.

fulvin catabolism(9), the finding was pertinent that both in rats(3) and humans(4) pretreatment with phenobarbital was followed by lower than control blood levels of griseofulvin.

In the present study pretreatment with primidone, another frequently used anticonvulsant, was found to cause a significant fall in the griseofulvin content in rat serum and livers. The effect was virtually the same as that with phenobarbital(3). It is, therefore, tempting to suggest that, as with phenobarbital, pretreatment with the structurally related primidone may accelerate the enzymatic breakdown of griseofulvin. Our data are compatible with the reports that primidone is metabolized to phenobarbital(10,11). However, they do not exclude the possibility that, like phenobarbital, primidone may affect *per se* the hepatic enzymes involved in drug metabolism.

In view of the similarity of effects of primidone and phenobarbital in rats and, since the depressing effect of phenobarbital on blood levels of griseofulvin has already been observed in human patients, it is likely that in humans primidone may cause the same.

Summary. Following oral administration significantly lower levels of griseofulvin were found in the serum and livers of rats pretreated with primidone. The fall was similar to that produced by phenobarbital. It is likely that primidone, like phenobarbital, accelerates the catabolism of griseofulvin.

We wish to acknowledge with gratitude the many stimulating discussions with the late Dr. Richard Carey.

1. Anderson, D. W., Ann. Allergy, 1965, v23, 103, and references cited therein.

2. Kraml, M., Dubuc, J., Dvornik, D., A.M.A. Arch. Dermatol., 1963, v87, 179, and references cited therein.

3. Busfield, D., Child, K. J., Tomich, E. G., Brit. J. Pharmacol., 1964, v22, 137.

4. Busfield, D., Child, K. J., Atkinson, R. M., Tomich, E. G., Lancet, 1963, v2, 1042.

5. Kraml, M., Dubuc, J., Beall, D., Canad. J. Biochem., 1962, v40, 1449.

6. Kraml, M., Dubuc, J., Dvornik, D., J. Pharm. Sci., 1965, v54, 655.

7. Bedford, C., Child, K. J., Tomich, E. G., Nature, 1959, v184, 364.

8. Conney, A. H., Burns, J. J., Advances in Pharmacology, Garatini, S., Shore, P. A., eds., Academic Press, N. Y., 1962, v1, 31, and references cited therein.

9. Barnes, M. J., Boothroyd, B., Biochem. J., 1961, v78, 41.

10. Butler, T. C., Wadell, W. J., Proc. Soc. Exp. Biol. and Med., 1956, v93, 544.

11. Plaa, G. L., Fujimoto, J. M., Hine, C. H., J. Am. Med. Assn., 1958, v168, 1769.

Received September 9, 1965. P.S.E.B.M., 1965, v120.

Experimental Infection of Calves with a Bovine Adenovirus.* (30623)

SASHI B. MOHANTY AND MARY G. LILLIE
Department of Veterinary Science, University of Maryland, College Park

Adenoviruses, as a group, are often found as the cause of acute respiratory illness in man. These viruses have been demonstrated in the eye, nasopharynx and intestinal tract of man and some animals. Neutralizing antibodies to various types of adenoviruses have been demonstrated in bovine sera(1,2). Two strains of adenovirus which are antigenically related to human adenoviruses(3,4), have been isolated from the feces of apparently healthy cows. This report is concerned with clinical and serological response of calves after exposure to a strain of bovine adenovirus by various routes of inoculation.

* This investigation was supported by U.S.P.H.S. Grant AI-03149 from NIH, Nat. Inst. of Allergy and Infect. Dis.

Approved as Scientific Article No. A 1223; Contribution No. 3723 of Maryland Agri. Exp. Station.

Materials and methods. Virus. A bovine adenovirus (strain 10088) was obtained from Dr. M. Klein, Dept. of Microbiology, School of Medicine, Temple University, Philadelphia, Pa. Identifying properties of this virus as