act by competing with a pyridoxine-like compound for a position in some enzyme system of the parasite. Interestingly, Silverman and Evans[1] have reported that while certain polyamines will antagonize the growth inhibitory action of atabrine on *Escherichia coli in vitro* pyridoxine under their experimental conditions failed to effect the action of atabrine.

Summary. Pyridoxine when administered in doses several thousand times greater than required for the nutrition of the host will inhibit the activity of minimal effective doses of quinine and of atabrine against *P. lophuræ* infections in Pekin ducklings.

1 Silverman, Milton, and Evans, E. A., Jr., *J. Biol. Chem.*, 1943, **150**, 265.

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Elevated Plasma Fibrinogen Levels and Liver Necrosis in Rats Receiving Atabrine.*

R. H. SILBER, I. CLARK, AND H. SIEGEL. (Introduced by H. Molitor.)
From the Merck Institute for Therapeutic Research, Rahway, N.J.

Wright and Lillie[1] and Siegel and Mushett[2] have reported the appearance of necrotic areas in the livers of rats receiving atabrine. Scudi and Hamlin[3] studied the effect of atabrine on dogs and rats fed purified diets varying in protein content and suggested that an increase in plasma fibrinogen in their animals was a result of liver damage. This study has been extended to establish the correlation between the increase in plasma fibrinogen and the presence and extent of liver damage in individual rats dosed with atabrine.

Experimental and Results. Ninety-two rats, weighing 120 to 250 g each, were given 150 mg of atabrine per kg by stomach tube three times weekly. At intervals of 1 to 4 weeks, rats were sacrificed and examined for liver necrosis. Plasma fibrinogen levels of all animals, including 75 untreated controls, were determined by the method of Cullen and Van Slyke.[4]

The plasma fibrinogen levels of these rats were as follows: 75 untreated controls averaged 212.5 ± 4.2† mg % (range 135-300); 50 atabrine dosed rats showing no evidence of gross liver necrosis, 232 ± 4.8 mg % (range, 160-320); and 42 atabrine-dosed rats which had gross liver necrosis, 384.4 ± 12.3 mg % (range 240-570). Thus, in the treated group which did not show grossly necrotic livers there was a slight but significant increase in plasma fibrinogen over the level found in the untreated controls. A much more striking elevation in plasma fibrinogen accompanied the development of gross liver necrosis.

The body weight of the rats appeared to be a predisposing factor in the development of liver necrosis since the damage occurred earlier in large rats, as shown in Table I.

In the group of rats with an average initial weight of 120 g (Table I), dosed 3 times weekly, liver necrosis began to develop during the 6th week. In a second group of rats of the same initial weight but receiving only 2 doses per week, liver necrosis became apparent during the 6th week even though these animals received only two-thirds the total number of doses administered to the first group. This may be explained by the fact that the blood levels of both groups averaged about 5 γ per cc. Therefore, in these rats, the occurrence of liver necrosis was more a function of

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1 Wright, C. I., and Lillie, R. D., *Public Health Rep.*, 1943, **58**, 1242.

2 Siegel, H., and Mushett, C. W., in press.

3 Scudi, J. V., and Hamlin, M., *J. Pharm. and Exp. Therap.*, 1944, **80**, 150.

4 Cullen, G. E., and Van Slyke, D. D., *J. Biol. Chem.*, 1920, **41**, 587.

† Standard error.

TABLE I.
Liver Necrosis and Fibrinogen Levels in Rats of Different Weights Dosed with 150 mg of Atabrine per kg 3 Times per Week.

Initial wt. in g	No. of rats	No. of doses	Incidence of liver necrosis, %	Avg level of fibrinogen, mg%
120	15	10	0	220
155	19	9	5	260
180	5	8	60	325
210	7	8	100	440
245	7	8	100	550

time than total dose of atabrine.

With prolonged dosing, the liver necrosis became more extensive and the plasma fibrinogen levels higher. Thus, in the above group which was dosed twice weekly, those rats showing necrotic livers after 5 weeks had an average fibrinogen level of 300 mg %; after 9 weeks, 365 mg %; and after 10-13 weeks, 460 mg %.

Discussion. Foster and Whipple[5] have shown that, although certain types of liver damage, such as that induced by chloroform or phosphorus, depress plasma fibrinogen levels, the level is elevated in a variety of other pathological conditions. They state that " . . . tissue injury unaccompanied by the usual inflammatory reaction is sufficient to give this specific physiological reaction—an overproduction of fibrin in the body." However, in their study of plasma fibrinogen levels in animals with damaged livers, elevated fibrinogen levels were observed only after very limited exposure to chloroform or phosphorus. Prolonged treatment invariably resulted in depressed fibrinogen levels. In contrast to this condition, the atabrine-dosed rats described in this paper showed no decrease in fibrinogen levels. A slight increase was found prior to the development of gross areas of necrosis in the liver. The histopathological picture at this stage, namely, early degenerative changes preceding gross liver necrosis, could easily be compared with that found in the early stages of liver damage caused by chloroform or phosphorus.[2] With prolonged dosing this necrotic condition became more extensive and was accompanied by correspondingly increased plasma fibrinogen levels, with maximal levels obtained when as much as two-thirds of the liver were involved, although in advanced stages of liver poisoning by other agents the plasma fibrinogen levels are low.

The earlier appearance of necrotic areas in the livers of large rats raised the question of the validity of toxicity comparisons in rats of different weights, dosed on a body weight basis. Since the liver is the principal organ damaged by the administration of atabrine, it seemed possible that a change in the ratio of liver weight to body weight might account for this difference in toxicity. The livers of rats weighing 100 to 107 g constituted approximately 4.3% of their body weight; those of 180 to 225 g rats, 3.2%; and of 250 to 465 g rats, 2.5%. Consequently, when doses of 150 mg per kg were administered, a 100 g rat actually received 3.5 mg per g liver whereas a 300 g rat received 6 mg per g liver. It is not surprising that under these conditions the livers of heavy rats developed necrosis first.

Summary. The increase in plasma fibrinogen levels in rats receiving atabrine has been correlated with the presence and degree of necrosis in the liver.

The maintenance of a blood level of about 5 γ per cc in 120 g rats was sufficient to induce gross liver damage after 5 weeks, irrespective of the number of doses given.

When dosed on a mg per kg basis, older rats appeared to have a decreased tolerance to atabrine poisoning. Evidence has been presented to show that the decrease in the ratio of liver weight to body weight with age may account for the earlier onset of liver damage in older rats.

[5] Foster, D. P., and Whipple, G. H., *Am. J. Physiol.*, 1922, **58**, 407.