silver sections taken from congenitally abnormal brains, in which the telencephalon is largely absent but the infratentorial regions normal, no trace of a pyramidal system can be detected.[10] It is obvious, therefore, that Marie and Guillain's conjecture that fibers from the brain stem itself contribute to the pyramidal system must be incorrect, at least with regard to infratentorial levels.

We may now ask whether the diencephalon contributes any fibers to the system. If all the cortex and corpus striatum are removed from an animal (case J 31, the physiologic, cytologic, and myelinated fiber features of which have been previously reported[11]) silver stains again reveal no fibers in the pyramids. The same is true of silver examinations made upon a monkey lacking only cortex and putamen (case J 33, other studies of which have been published[12]). We can, in fact, state that the small pyramidal fibers are definitely of cortical origin for silver studies of the pyramids of our case 36, from which only cortex had been removed,[13] have also failed to disclose any sound pyramidal fibers in silver section.

Conclusion. Practically all the heavily myelinated fibers in the pyramids of the monkey's brain arise from the region of the cerebral cortex in which the gigantopyramidal cells of Betz are found. Since we know that all of these fibers cannot be accounted for as arising from such cells they must also come from smaller elements. The fact that Weigert material fails to show any fibers in the pyramids after ablation of the precentral gyri, does not prove that the pyramids are devoid of fibers for smaller elements can plainly be seen with silver stain. Since no fibers remain after removal of all of the cortex none of these smaller fibers can be attributed to an infrapallial origin.

[10] Marburg, O., and Mettler, Fred. A., *J. Neuropath. and Exp. Neur.*, 1943, **2**, 54.

[11] Mettler, Fred. A., *J. Comp. Neurol.*, 1943, **79**, 209.

[12] Mettler, Fred. A., *J. Comp. Neurol.*, 1943, **79**, 204.

[13] Mettler, Fred. A., *J. Comp. Neurol.*, 1943, **79**, 195.

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Effect of Pyridoxine on Activity of Quinine and Atabrine Against *Plasmodium lophuræ* Infections.

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In an investigation of the effect of large amounts of vitamins on the activity of quinine and atabrine in avian malaria it was found that massive doses of pyridoxine markedly inhibited the activity of these drugs against *Plasmodium lophuræ* infections.

Pekin ducklings weighing about 50 g each were inoculated intravenously with 10,000,000 erythrocytes parasited by *P. lophuræ*. The ducks were allowed to feed at will on a commercial starting mash. In all experiments quinine sulfate and atabrine dihydrochloride were administered as aqueous solutions into the crops by tube once daily for 6 days beginning on the day of inoculation. Pyridoxine hydrochloride was given in the same manner in most of the experiments but as is indicated on the accompanying tables it was in certain cases administered subcutaneously. Since both quinine and pyridoxine are excreted quite rapidly they, although given individually, were always administered within an interval of about 30 minutes. Blood smears were made on the seventh day after inoculation and the number of parasitized erythrocytes per 10,000 erythrocytes was determined.

Pyridoxine when given in a large daily dose produced almost complete inhibition of the

TABLE I.
Effect of Pyridoxine on Activity of Quinine Against the Schizonts of *P. lophurœ*.
5 ducks in each experiment.

Exp. No.	Drug	Dose, mg/kg	Route	% of erythrocytes parasitized on 7th day
1	Quinine	15	p.o.	1.5
	Quinine + Pyridoxine	15 500	p.o.	33.2
	Pyridoxine	500	p.o.	46.5
	Controls	—	—	51.1
2	Quinine	20	p.o.	1.5
	Quinine + Pyridoxine	20 500	p.o.	33.8
	Pyridoxine	500	p.o.	32.7
	Controls	—	—	40.8
3	Quinine	10	p.o.	0.3
	"	15	p.o.	0.02
	Quinine + Pyridoxine	10 200	p.o. s.c.	39.1
	Quinine + Pyridoxine	15 200	p.o. s.c.	5.9
	Pyridoxine	200	s.c.	74.2
	Controls	—	—	66.5

TABLE II.
Effect of Pyridoxine on Activity of Atabrine Against the Schizonts of *P. lophurœ*.
5 ducks in each series.

Exp. No.	Drug	Dose, mg/kg	Route	% of erythrocytes parasitized on 7th day
1	Atabrine	5	p.o.	2.68
	Atabrine + Pyridoxine	5 500	p.o.	48.7
	Pyridoxine	500	p.o.	46.5
	Controls	—	—	51.1

activity of quinine and atabrine at the dose levels used (Table I and II). The doses of quinine and atabrine used in these experiments were selected because experience had shown them to be approximately the minimal amounts necessary for suppression of the disease. The dose of pyridoxine was chosen arbitrarily and although the exact requirement is not known it probably represented several thousand times the amount of vitamin needed by the duckling for optimal growth.

When pyridoxine was administered subcutaneously at 200 mg per kg it markedly inhibited the activity of a 10 mg per kg dose of quinine but was only moderately effective against a 15 mg per kg dose of quinine (Table I). This experiment showing that the inhibiting power of a unit dose of pyridoxine varies with the amount of quinine involved suggests that there may be a quantitative relationship but the exact nature of this relation remains for further study.

In the experiments in which both the antimalarials and pyridoxine were given by mouth within a short interval it was conceivable that the inhibition might have been due to a direct interaction in the intestinal tract before complete absorption had occurred. This explanation seems unlikely in view of the experiment in which the pyridoxine was shown to have inhibiting power even when it was administered subcutaneously and the drug given by mouth.

The fact that pyridoxine inhibits the action of quinine and atabrine on *P. lophurœ in vivo* suggests the possibility that pyridoxine or a compound of similar structure is essential for the parasite and that quinine and atabrine

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.*

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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.