TABLE I. Effect of Pretreatment with Tranylcypromine or Iproniazid and Subsequent Injection of Tryptamine upon Brain Tryptamine Levels and Convulsive Activity.

	Iproniazid		Tranylcypromine			
Dose (mg/kg)	25		0.36		0.72	
Pretreatment time (hr)	5	17	5	17	5	17
	Tryptamine conc., μg/g brain (clonic convulsions)*					
	1.080 (+3)	.902 (+3)	.218 (1)	.411 (+3)	1.30 (+3)	.504 (+3)
	.460 (+3)	.779 (+3)	.200 (0)	.175 (0)	.938 (+3)	.451 (+3)
	.648 (+3)	.888 (+3)	.145 (0)	.350 (1)	.699 (+3)	.348 (+3)
	.845 (+3)	.478 (+3)	.500 (+3)	.217 (0)	.856 (+3)	
	.669 (+3)	.605 (+3)	.164 (1)	.388 (+3)	.612 (+3)	
			.059 (0)	.278 (2)	.936 (+3)	
			.195 (1)		.768 (+3)	
					.369 (+3)	
					.252 (+3)	

Dose refers to oral administration of tranylcypromine and iproniazid at indicated time prior to intrav. inj. of tryptamine (5 mg/kg).

* No. in parentheses represents duration of clonic convulsions, in sec. In all cases of (+3), clonic convulsions were sustained beyond 3 sec. and, in most cases, were very marked. Convulsions were elicited 30-40 sec. after tryptamine inj. and animals were sacrificed 60-75 sec. after inj. Control values of tryptamine concentration (μg/g ± S.E.M.):

Normal, .032 ± .002 (N = 14); after either drug (N = 10), same as normal; after tryptamine, .173 ± .019 (N = 10).

tion of tryptamine into rats pretreated with either of above monoamine oxidase inhibitors were correlated with increased concentration of amine in the rat brain. In view of demonstrated ability of systemically injected tryptamine to penetrate rat brain, it is reasonable to conclude that the elicited pharmacologic effects reflected a central mechanism of action of the amine, potentiated by inhibition of brain monoamine oxidase activity.

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Properdin Titers of Dogs Surviving Hemorrhagic Hypotension.* (25763)

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Attention has been called to a relationship between serum properdin levels and hemorrhagic shock(1). It was demonstrated that properdin titers, measured by the zymosan assay, dropped progressively during oligemic and post-transfusion periods of shock. More recently, by phage neutralization assay, titers decreased after hypotensive period had been terminated(2). In these studies, duration of hemorrhage was quite prolonged, and all animals died. To explore further the relationship between properdin and hemorrhagic shock, duration and intensity of hemorrhage was utilized so that approximately 50% of dogs survived. A second group of dogs was subjected to more severe conditions of hypotension so that irreversibility might be expected in virtually all cases. These animals,

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TABLE I. Comparison of Data on Surviving and Non-surviving Dogs.

	No. of dogs	Max bleeding vol, ml/kg	% take up	Survival, hr	Ph.N_{50}/ml properdin titer Control	% control at 6½ hr
Survivors	7	51.3 ± 12.9*	11.6 ± 9.5	†	27.6 ± 8.5	83.7 ± 10
Non-survivors	8	49.7 ± 8.5	18.7 ± 9.9	14.9 ± 3.4	23.0 ± 7.	62.7 ± 13.6
P value		.8	.2		.3	<.01

* Mean ± stand. dev. † Lived beyond 3 days.

however, were treated by perfusion of intestine through the superior mesenteric artery. Some dogs survived, and properdin studies are presented here.

Methods. Fifteen dogs, weighing 11 to 18 kg, were deprived of food but not water, for 24 hours. They were given 30 mg morphine sulfate intramuscularly one hour before experiment. Procaine was injected locally, and using aseptic technic, both femoral arteries and femoral vein were cannulated. Heparin,† 2 mg/kg i.v. was administered, and additional 5-10 mg given at end of first hour of oligemia. One artery was connected to mercury manometer and the other to sterile graduated reservoir. The animal bled into the reservoir until its arterial pressure fell to 35 mm Hg. Blood pressure was maintained at this level for 135 minutes, by automatic device(3). At end of oligemic period, the blood remaining in reservoir was returned to the dog. Twenty ml samples of blood were taken 5 min. before oligemia, 3-5 min after return of reservoir blood and 6½ hours after start of hemorrhage. Additional bleedings were taken from surviving animals at approximately daily intervals. Blood samples were centrifuged in the cold. Plasma was placed in sealed tubes and stored at −30°C. The phage neutralization method was used to determine properdin titers(4). Activity is expressed as 50% neutralizing units/ml of undiluted plasma (Ph.N_{50}).‡ Hemodynamic data from second group of dogs has been described(5). These animals were subjected to a severity of hemorrhage which ordinarily produces irreversibility. They were kept at 35 mm Hg arterial pressure until they took back 40% of their maximum shed blood volume, or until they had been in oligemia 4-5 hours. In addition, their intestinal vascular beds were perfused with arterial blood at approximately normal rate of flow. Of 7 surviving dogs, 2 had been autoperfused and 5 were donor cross perfused. Many more of perfused dogs died than survived. Data from 6 representative non-survivors are included in this report.

Results. Table I includes data from the 15 dogs subjected to 135 minutes of hypotension at 35 mm Hg arterial pressure. Comparison of results indicates that the only significant difference ($P<0.01$) is that properdin titers 6½ hours after start of hemorrhage decreased to a greater extent in non-survivors.

Fig. 1 records percent change in properdin titer for each dog in terms of its control titer. At the end of hypotensive period (2¼ hr), there was no significant difference between survivors (open circles) and non-survivors (solid triangles). At 6½ hr, however, the percentage decline in properdin titers fell to considerably greater extent in animals which did not survive. The 2 non-survivors which lived 24 and 36 hours showed continued decline in properdin titer (dashed lines). On the other hand, titers of survivors remained at approximately the 6½ hour level until 24 hours had elapsed. Between 24 and 48 hours, level in surviving animals increased to approximately control range. They reached a peak, which in most cases was well above control level, between 4th and 8th day, then started to decline toward control.

Fig. 2 represents properdin levels of 2 autoperfused and 5 donor cross-perfused survivors together with 6 similarly treated non-survivors. Non-survivors had lower properdin titers in immediate post-transfusion period than surviving group. Levels in survivors usually rose to above control within a few

† Heparin supplied thru courtesy of Lilly Labs.

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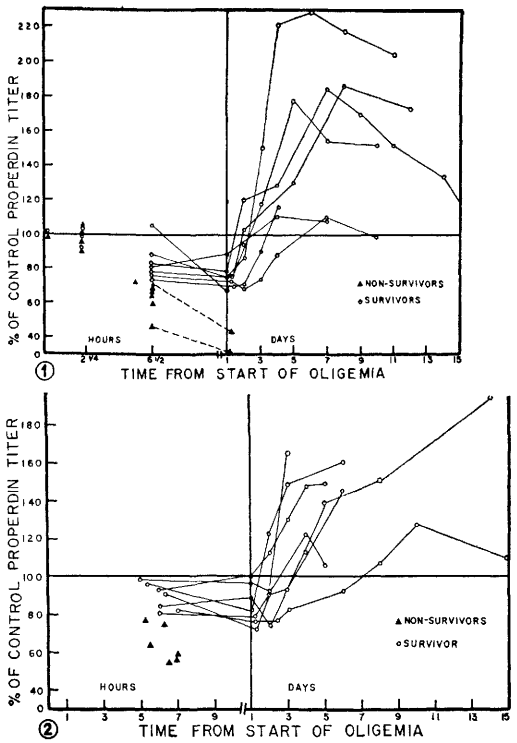

FIG. 1. % of control properdin titer of dogs subjected to hemorrhagic shock at 35 mm Hg arterial pressure for 135 min.

FIG. 2. % of control properdin titer of perfused dogs subjected to severe conditions of hemorrhagic shock.

days and followed the general pattern of survivors in Fig. 1. In perfused dogs, control properdin level was 25.1 ± 12.3 $Ph.N_{50}$ units/ml for survivors and 22.5 ± 9.1 for non-survivors. Duration of oligemia was the same for both groups, 3.8 ± 1 hours.

Discussion. During 135 minutes of oligemia, there was no detectable alteration in serum properdin titer (Fig. 1). The titer declined appreciably, however, 255 minutes after reinfusion of shed blood. This pattern was identical with that reported previously(2) using the same assay.

Initial fall and subsequent rise of properdin titers supplement one of the predominant hypotheses currently invoked to explain hemorrhagic shock. Convincing evidence has been adduced which demonstrated that during oligemia there is a rise in endotoxin content of blood serum(6), and these endotoxins are in some way responsible for resultant lethal outcome(7). The endotoxins are polysaccharides and are probably largely derived from the Gram negative bacteria of intestinal flora(7). Furthermore, bacterial endotoxins are capable of combining with properdin and quantitatively reduced its activity(8).

It may be postulated that endotoxins are formed and combine with properdin to produce reduction in titer during post-transfusion phase. The level of properdin may thus be an inverse measure of amount of endotoxin present. It may be observed that 6½ hours after inception of hemorrhage (Fig. 1) dogs having lowest properdin titer (most endotoxin?) did not survive.

The subsequent rise in properdin level in surviving animals may be due to the stimulating (perhaps antigenic) effect of abnormal amounts of endotoxin resulting from oligemia. Injections of polysaccharides(9) as well as bacterial endotoxin(10) give rise to increased properdin titers. A similar relationship between zymosan and bactericidal activity was previously reported(9) and it was suggested that the polysaccharide stimulated production of antibodies with receptor configurations similar to those found in properdin of normal serum.

Summary. Fifteen dogs were bled to mean arterial pressure of 35 mm Hg for 135 min, after which shed blood was reinfused. Seven animals survived longer than 72 hours. Serum properdin levels fell in all dogs during post-transfusion phase but titers of non-survivors were significantly more depressed than those of survivors. In survivors, properdin levels rose during next few days and reached a level considerably above control by 4th to 8th day, then started to decline toward control. Dogs subjected to more severe conditions of hypotensive shock but perfused by way of superior mesenteric artery showed a similar pattern.

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Reduced Caries in Offspring of Rats Receiving Tetracycline* During Various Prenatal and Post-Partum Periods. (25764)

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It has been shown that aureomycin (chlortetracycline) inhibits caries in the rat when added to a caries-test diet after weaning(1,2). The present communication demonstrates the effectiveness of tetracycline in markedly reducing caries activity in offspring of mothers receiving the antibiotic during various prenatal and post-partum periods.

Methods. Sprague-Dawley rats were bred and insemination was diagnosed by vaginal smear. The animals were then divided into 4 groups. Groups A, B, and C received a solution containing 2.5 mg of tetracycline hydrochloride† per ml prepared fresh 3 times weekly, and Group D received distilled water. Group A received the antibiotic during gestation only (21 days); Group B, during gestation and 14 days of lactation; and Group C, during gestation, lactation and the remaining 7 days of the preweaning period. Group D received distilled water during gestation, lactation and until the offspring were weaned at 21 days of age. Purina laboratory chow was available during gestation and lactation and "non-cariogenic" Diet 550(3) was offered thereafter until the offspring were weaned. The offspring were then housed 2 per cage by sex and received distilled water and caries-test Diet 636(4) *ad libitum* for 60 days. Food and fluid intakes of mothers and offspring were recorded. The heads were cleaned of soft tissue using the dermestid beetle(5), and the teeth were scored for caries(6). The data are presented in Table I. A preliminary investigation which prompted the present extended study was comprised of groups similar to B and D, and the data are presented in Table II.

Results. Tetracycline did not affect fluid consumption of the mothers although the pH of the antibiotic solution was 3.0 (Tables I, II). In addition, tetracycline showed no adverse effect on litter production. Average number of offspring per litter for the 4 groups in Table I was 8.0, 10.6, 9.7 and 8.7 respectively. Because a portion of each litter was reserved for a separate study, only about half of each litter is represented. Tetracycline did not adversely affect weight gains or diet and fluid intakes of the offspring during the 60-day post-weaning experimental period. In the preliminary study (Table II), the control and experimental groups had 7.0 and 9.5 offspring per litter. Weight gains, diet and fluid intakes were somewhat less than in the expanded study. These findings are of interest because Keyes(7) found high mortality in hamsters born of mothers receiving penicillin during gestation and the first week of lactation. Rats appeared to show a better tolerance to penicillin(7).

In the present studies, the most striking effects of administration of tetracycline were

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† Stability of tetracycline hydrochloride as administered to the rat in drinking water was determined spectrophotometrically daily for 3 days. The characteristic spectrum(8) remained unchanged but optical density at the 2 maxima of 276 and 356 mu were depressed 9.7% and 9.4% respectively.