tier(6) who observed a fusion of the QRS of an ectopic complex with the T wave of the preceding beat at the onset of ventricular fibrillation. In the present study this simultaneous occurrence of a QRS with the preceding T wave has also been identified before experimental ventricular fibrillation. However, in addition there was the accompanying increase in the duration of the QT interval prior to the onset of the ventricular arrhythmias. These electrocardiographic changes gave a picture suggesting a delay in the repolarization processes of the ventricular myocardium after petroleum ether and epinephrine. Thus, the entrance of an impulse initiated by epinephrine from an ectopic focus into the remaining myocardium at a time when the ventricles were vulnerable to fibrillation appeared to be an important factor in the precipitation of ventricular fibrillation by these agents.

Taken together these observations suggested that petroleum ether and epinephrine increase the vulnerability of the ventricles to fibrillation by inhibiting the biochemical processes responsible for the repolarization of the ventricular myocardium. In support of this view was the observation that isoproterenol did not increase the QT interval after petroleum ether, and this catecholamine also failed to precipitate ventricular arrhythmias in these preparations.

Summary. An increase in the QT interval and the QT/RR ratio was observed prior to the onset of multiple focal ventricular tachycardia and fibrillation induced by petroleum ether and epinephrine or norepinephrine in cats under pentobarbital anesthesia. This prolongation of the QT interval before experimental ventricular tachycardia and fibrillation was significantly greater than that produced by these catecholamines in the absence of arrhythmias. Isoproterenol, which did not lead to ventricular tachycardia after petroleum ether, also failed to increase the duration of the QT interval. The appearance of the electrocardiogram preceding these experimental arrhythmias suggested that a delay in the repolarization of the myocardium was a factor in the precipitation of ventricular fibrillation during hydrocarbon-catecholamine syncope.

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Effect of *Salmonella typhosa* Endotoxin on Perfused Dog Spleen.* (28425)

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Changes in calculated vascular resistance following injection of endotoxin in various vascular beds perfused at constant blood flow have been reported(1-7). The forelimb(1), lung(3), stomach(5), and kidney(6) demonstrated increased resistance while the coronary vasculature(4) responded with a decrease. Earlier reports suggested that the immediate systemic hypotension following lethal doses of endotoxin resulted from hepatic and intestinal congestion(2,7). Hepatic venoconstriction and engorgement are of short duration; however, intestinal pooling persists(2, 7). Even though the gastric and intestinal circulations are contiguous, the responses of the veins to endotoxin are apparently dissimilar. The stomach behaves more like the

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liver; that is, marked increases in calculated resistance and venous pressure occur 5 to 10 minutes after endotoxin administration, only to return toward control values by 30 minutes(5).

Since the spleen is also in direct continuity with the portal circulation, and because the dog spleen is able to store or release a large volume of blood, it was of interest to determine whether the splenic response is similar to that of the intestine or to the gastric-hepatic vascular beds. If splenic and intestinal responses were alike, venous pressure should remain persistently elevated(8) and result in massive splenic congestion. If, on the other hand, the splenic vascular bed responded more like the liver and stomach, there would be only an initial transient period of congestion and increased venous pressure.

This paper reports changes in resistance to blood flow through the vascular bed of the constantly perfused dog spleen following local administration of lethal doses of the lipopolysaccharide of *Salmonella typhosa* endotoxin.

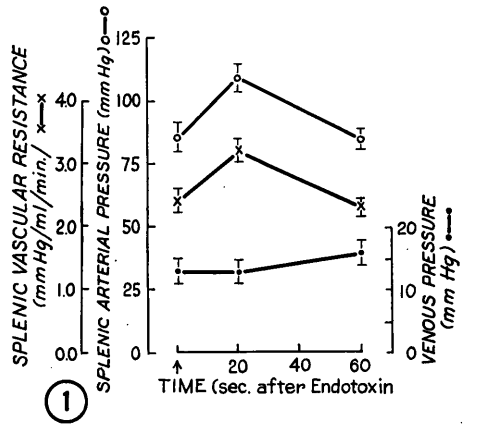
Materials and methods. Ten mongrel dogs weighing between 12.7 and 18.0 kg were studied acutely. The animals were anesthetized with pentobarbital; heparin was administered intravenously. Following a left flank incision the splenic artery and vein were identified, and the pancreatic, gastric, and mesenteric branches of these vessels were ligated. A blood pump was then interposed between the right femoral and splenic arteries, and adjusted to give a constant flow of 30 ml/min. The extracorporeally circulated arterial blood was maintained at 37°C by diverting the tubing through a water bath. Particular care was taken to leave the periarterial nerves intact during the ligation and cannulation of the splenic artery; the splenic vein remained undisturbed. Even though previous studies (9) had demonstrated the stability of the preparation, 3 of the 10 animals served as technique controls. The remaining 7 dogs were given endotoxin.

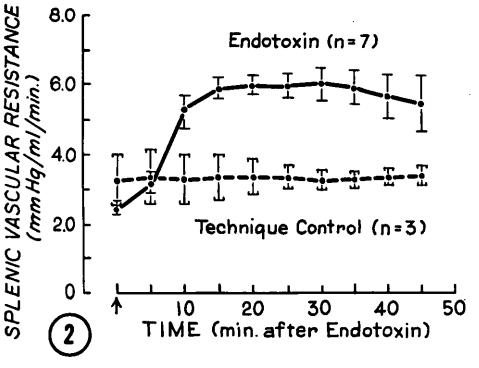
Pressures in the splenic artery and vein and a carotid artery were recorded continuously by means of Statham pressure transducers connected to a direct-writing oscillograph. Splenic artery pressures were measured from the perfusion tubing just proximal to the cannula. Splenic vein pressures were obtained by direct needle puncture of the vein in the splenic pedicle. Vascular resistance was calculated from the quotient of the arterio-venous pressure difference divided by blood flow and expressed as mm Hg/ml/min.

A 20 minute stabilization period followed the onset of splenic perfusion and the subsequent 45 minutes comprised the experimental observation period. At zero time, 0.6 mg/kg of *S. typhosa* endotoxin was injected in one bolus into the perfusion tubing and the vascular responses were recorded. The 3 technique control animals were given injections of one ml of pyrogen-free water.

Results. The response of the splenic artery and vein pressures, as well as calculated vascular resistance, during the first minute after endotoxin injection is shown in Fig. 1. In each of the 7 animals splenic artery pressure transiently increased significantly and then returned to control, pre-injection levels. Twenty seconds after endotoxin injection an average peak splenic artery pressure of 110 mm Hg was reached (27% above control), and by one minute returned to the pre-injection level of 86 mm Hg. This phenomenon was not observed in any of the control animals receiving pyrogen-free water or in other animals receiving hypertonic solutions. In each animal venous pressure remained unchanged during the initial 20 seconds, and only increased at the end of the first minute, at which time venous pressure was 16 mm Hg.

The average values for calculated splenic vascular resistance at 5 minute intervals for both control and endotoxin-treated groups is shown in Fig. 2. There was no significant change in splenic vascular resistance or systemic arterial pressure during the 45 minute observation period in the 3 technique control animals receiving pyrogen-free water. The endotoxin treated group, however, demonstrated a progressive increase in calculated splenic vascular resistance over the initial 15 minutes. Average increases for the 7 animals were 32, 116, and 145% at 5, 10, and 15 minutes, respectively. Vasoconstriction persisted throughout the observation period so





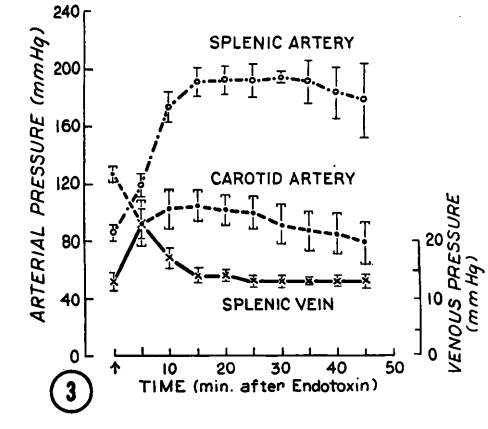


FIG. 1. Splenic artery and vein pressures and vascular resistance during the first minute following injection of endotoxin into splenic artery. Each curve represents avg ± 1 standard error of mean of 7 animals.

FIG. 2. Effect of endotoxin on splenic vascular resistance as a function of time. Endotoxin curve represents avg ± 1 standard error of mean (SEM) of 7 animals. Technique control curve represents avg ± 1 standard error of mean of 3 animals receiving pyrogen-free water.

FIG. 3. Effect of endotoxin on splenic artery and vein pressures and mean carotid artery pressure averaged from the 7 animals of the *in situ* preparation. Bars represent ± 1 standard error of mean.

that at 30 and 45 minutes the resistance values were still 150 and 128%, respectively, above control levels.

The increased resistance was reflected by increases in splenic artery pressure (Fig. 3). Average pre-endotoxin splenic artery pressure was 86 mm Hg; and at 5, 10, 15, 30, and 45 minutes, pressures were 119, 174, 192, 195, and 179 mm Hg, respectively. Splenic vein pressures began to increase one minute after injection of endotoxin. Average pre-injection splenic venous pressure was 13 mm Hg, and at one minute following endotoxin injection had increased to 16 mm Hg. Venous pressure continued to rise, and by the fifth minute, averaged 23 mm Hg (77% greater than control). Venous pressure after 5 minutes began to fall so that 10 minutes following endotoxin, it was 17 mm Hg (31% greater than control), returning to pre-endotoxin levels by 25 minutes.

Systemic arterial pressure declined 27% in 5 minutes (from 127 to 83 mm Hg) and returned toward control levels by 15 minutes (105 mm Hg). Thereafter, average mean systemic arterial pressure continued to fall so that 30 and 45 minutes following endotoxin injection pressures were 92 and 79 mm Hg, respectively.

Discussion. The vascular responses observed within the first minute after endotoxin was injected are not unique to the spleen. A similar transient increase in calculated resistance was seen in the renal vascular bed (6), but was not observed in the stomach (5) and other vascular beds(1,3,4). The resistance increases in the spleen reflect arteriolar constriction, since at the time of peak response, 20 seconds, venous pressure was unchanged (Fig. 1). Venous pressure increased only after arterial pressure had returned to pre-endotoxin levels. Because the response occurred at 20 seconds arterial constriction could not have been produced by a systemic release of vasopressor agents. Preliminary work in this laboratory on this preparation confirms the findings of Green, *et al.*(10) that epinephrine and norepine-

phrine produce arteriolar constriction, increased venous pressure, and diminished splenic weight. Endotoxin, unlike catecholamines, evoked only arteriolar constriction. Hence, the initial transitory resistance increase was probably produced by a direct effect of endotoxin on the splenic arteriolar bed. A local release of some heretofore undescribed arteriolar constrictor is also possible.

The similar response of the splenic veins and the veins of the liver and stomach indicates that, in the portal circulation, persistent venoconstriction is unique to the intestine. Like the liver(2,7) and stomach(5) splenic venoconstriction occurs during the first 5 to 10 minutes, then returns to pre-endotoxin levels.

Previous studies, using phentolamine, have suggested that the total resistance increase may be explained by a systemic release of catecholamines(5,6). Unexplained, however, is the normal splenic venous pressure after 10 minutes coincident with arteriolar constriction. If a catecholamine release were the sole factor responsible for resistance increase, then venous and arteriolar pressures would remain elevated over the same time period. Unlike other vascular beds(1,3,5,6) splenic resistance remained elevated over the full 45 minutes without declining in the "late phase —after 15 minutes"(11).

Summary. These results demonstrate that local injection of the endotoxin *S. typhosa* into the splenic vascular bed of the dog, perfused at a constant flow, results in a progressive increase in calculated vascular resistance. The response of the splenic vasculature to lethal doses of endotoxin, furthermore, is unlike that of the intestine and resembles the response of other organs of the portal circulatory bed, the liver and stomach. Where a persistent venular constriction occurs in the intestine, only a transitory venoconstriction occurs in the spleen.

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Serum Proteins and Glycoproteins in 2 Strains of Mice Differing in Teratogenic Potential.* (28426)

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Protein metabolism has been implicated in teratology. Gillman *et al.*(1,2) suggested that altered behavior of the maternal proteins might be correlated with the teratogenic action of trypan blue on rabbit fetuses. Langman(3) found a greater risk of abnormal children in 19 pregnant women without evident disease but with altered serum protein fractions. Experimentally in rabbits, Langman and van Drunen(4) found, following trypan blue, increased α- and β-globulins in serum.

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