that either the increase in liver iron values was caused by changes in xanthine oxidase or that both the changes in liver iron and xanthine oxidase activity were an expression of some other unidentified cause. In addition, statistical analysis indicated that the changes in xanthine oxidase could not have accounted for all the variation in liver iron values, and cast doubt on the hypothesis of a causal relationship between xanthine oxidase activity and iron deposition in liver *in vivo*.

To avoid the many effects of ethionine and still produce a lowering of xanthine oxidase activity, the present experiments were set up utilizing sodium tungstate(7) as a means of depressing xanthine oxidase activity. Under these circumstances there was a definite decrease in xanthine oxidase activity but no histologic changes in the animals. Neither was there any difference in weight gain. When total carcass iron values were compared, the animals with low liver xanthine oxidase activity had the same amount of iron in the body as the pair fed control animals without the lowered xanthine oxidase activity. This indicated that there was no difference in absorption of iron in both groups. Neither was there any alteration in storage of iron in the liver (Table I). In addition, there was no lowering of hemoglobin values in the experimental animals, indicating that they did not suffer from anemia as a result of possible decrease in release of body storage iron. It was concluded from these studies that the lowering of liver xanthine oxidase activity did not affect iron deposition in the liver or iron absorption. Recently Strohmeyer, *et al.*(8) utilizing a different approach failed to demonstrate a relationship between liver xanthine oxidase activity and iron metabolism. It would seem from our study that whatever role the liver xanthine oxidase may play in iron metabolism it has no direct effect on liver iron storage or on iron absorption.

Summary. Sodium tungstate was added to the diet to decrease liver xanthine oxidase activity. There were no concomitant changes in liver iron or iron absorption associated with the decrease in xanthine oxidase activity.

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Changes in Total Peripheral Resistance in Endotoxin Shock.* (26834)

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Previous reports have described changes in total peripheral resistance during irreversible hypotension following injection of endotoxin(1-5). Results, however, have differed and the question of resistance changes in endotoxin shock is not settled. Two general procedures have been previously employed for calculation of vascular resistance: (a) measurements of arterial pressures during constant cardiac inflow in perfused animals (3,4), and (b) measurements of arterial pres-

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sure and cardiac output in intact animals administered endotoxin(1-3). These procedures are considered inadequate for several reasons: in the first instance, maintenance of a constant cardiac inflow during the post-endotoxin period may prevent significant alterations in resistance associated with neurohumoral or physical changes precipitated by severe hypotension(6-10). In the second instance a major difficulty arises in interpretation of resistance changes because of the tendency for resistance to increase as flow and distending pressure decrease(6,7). Since calculated total systemic resistance has been found to be more uniformly related to flow than to pressure(7), the present study was devised to control the parameter of flow (cardiac output). This study is considered important insofar as it provides a possible explanation for the development of irreversible shock.

Materials and methods. Studies were performed on 16 adult dogs weighing between 7.0 and 12.3 kg, anesthetized with sodium pentobarbital, 30 mg/kg. Animals were respired with room air provided by a constant pressure respirator. Aortic pressure was measured through a catheter inserted into the femoral artery connected to a Statham strain gauge and registered on a Sanborn direct writing recorder. A reservoir system was interposed between the central ends of the great veins (azygous vein ligated) and the right atrium, thus allowing direct measurement of the venous return. The system was primed with homologous heparinized blood. A sigmamotor pump returned the blood from the external reservoir to the right atrium. This procedure has been previously reported(3,4). Following cannulation of the right atrium and great veins the atrial inflow rate was repeatedly adjusted by altering the sigmamotor pump speed to maintain the venous reservoir at a constant volume. Within 30 minutes equilibrium was established and a 20 minute control period was begun. Flows during this period averaged 77 cc/min/kg body weight (range, 66-88). Cardiac inflow is assumed to equal cardiac output, under the conditions of these experiments(3,4). Venous return was periodically measured with cylinder and stop watch and a control period of constant flow was established for each preparation. Animals were divided into 3 groups: the first group consisted of 5 control animals in which the right atrial inflow exactly matched the venous return. The second group was composed of 6 dogs given a lethal dose of *E. coli* endotoxin‡ (0.55 mg/kg). In these dogs, as in the first group, the sigmamotor pump speed was varied so that venous return and cardiac inflow were equal. In a third series of 5 dogs endotoxin was not administered but the right atrial inflows were adjusted to approximate the average flows of the experimental group administered endotoxin. All experiments were terminated at 75 minutes beyond the control period due to development of excessive bleeding from cut surfaces, which interfered with the accuracy of the measurements.

Results. Fig. 1 illustrates the results from 5 dogs serving as controls and not administered endotoxin. There was no change in total peripheral resistance during the perfusion period although there was a gradual fall in both cardiac inflow and mean systemic arterial pressure. The results from this series served to evaluate the experimental procedure.

Fig. 2 provides mean values for 6 animals given endotoxin. Resistance remained fairly constant during the 35 minute period after endotoxin. Beyond this time there was a steady fall in resistance. Pressure and flow fell steadily until about 10 minutes after endotoxin, then rose to maximal values at about 25 minutes. Following this there was a steady drop in pressure with the cardiac inflow remaining relatively constant.

Fig. 3 gives results from 5 dogs not administered endotoxin, but having cardiac inflows matched with the mean flows of animals receiving endotoxin. Resistance rose following the initial reduction in flow and remained elevated until termination of the experiments. The drop in pressure after 25 minutes was more gradual than that shown in Fig. 2 which accounts for the differences in resistance between the latter 2 groups.

‡ Difco endotoxin.

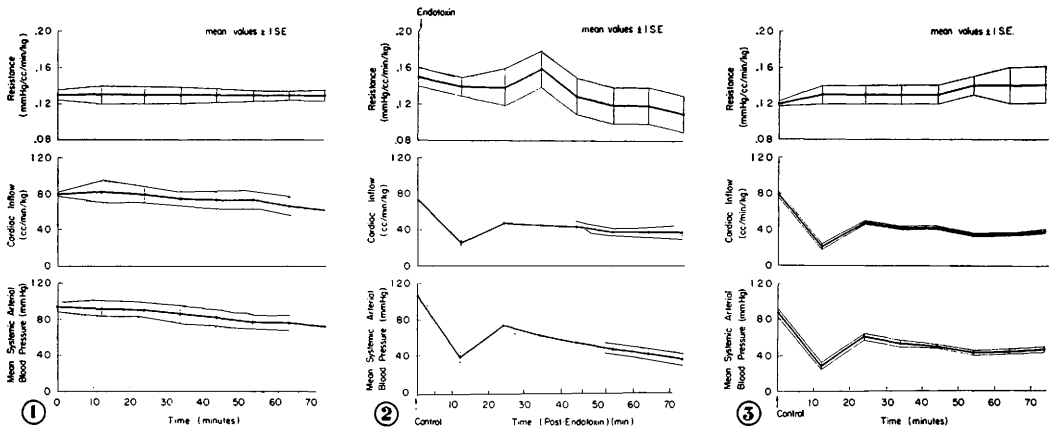

FIG. 1. Control experiments, showing changes in total peripheral resistance, cardiac inflow and mean systemic arterial blood pressure in 5 perfused dogs.

FIG. 2. Changes in total peripheral resistance, cardiac inflow and mean systemic arterial blood pressure in 6 perfused dogs administered lethal doses of endotoxin.

FIG. 3. Changes in total peripheral resistance, cardiac inflow and mean systemic arterial blood pressure in perfused dogs with artificially reduced cardiac inflows but not receiving endotoxin (see text).

Discussion. Evaluation of experimental technic. The procedure described appears to be useful in application to the general problem of total peripheral resistance changes in shock. The attempt was made (Fig. 3) to control the flow component of resistance(6,7) in order better to interpret the resistance changes at low cardiac inflows in animals administered endotoxin. Advantages of the procedure are the relative simplicity of the operative and perfusion technics and the convenient determinations of both flow and resistance. *Evaluation of results.* Findings show that the initial fall in blood pressure in dogs administered endotoxin is primarily due to a decrease in venous return. This is consistent with data obtained from constant cardiac inflow experiments(3). Following this period arterial pressure rises to a maximum at about 25 minutes, which is assumed to represent the period of "compensation", and appears to be brought about by an increase in venous return (Fig. 2). The data suggest that this maximal increase in mean systemic arterial pressure marks the onset of the irreversible phase of endotoxin shock, characterized by a progressive fall in total peripheral resistance and a steady decline in arterial pressure (Fig. 2). It has been reported(6,7) that resistance tends to increase as flow and distending pressure decrease, and on this basis one would expect that the resistance would rise in the later phase of endotoxin shock. That this did occur in animals not given endotoxin but whose cardiac inflows were artificially diminished (Fig. 3) indicates that the decline in peripheral resistance in animals in endotoxin shock assumes a more prominent role. It is apparent from this study that the vascular response of the endotoxin animals is inadequate to support the systemic arterial pressure, and that a decrease in vessel tone has occurred. Recent findings in this laboratory(8-10) suggest that both neural and humoral factors may be responsible for the fall in systemic resistance.

Summary. A series of experiments has been carried out on dogs to determine total peripheral resistance changes in endotoxin shock. Animals were perfused with homologous heparinized blood at controlled and measured cardiac inflows. Results suggest that the onset and course of irreversible shock are characterized by a progressive fall in total peripheral resistance. The mechanism of the decline in resistance has been suggested by earlier studies from this laboratory.

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Effects of Pretreatment with Antibiotics on Survival Following Mesenteric Arterial Occlusion in Rats. (26835)

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Recent studies have shown that changes in the intestinal tract are largely responsible for the irreversible course of the syndrome initiated by hemorrhagic, traumatic, and septic shock. Fine *et al.*(1,2) and Lillehei(3) have provided evidence indicating that the primary factor in this regard in the rabbit and dog is the systemic dissemination of bacterial products derived from the intestinal flora.

It appeared to us that the shock induced by temporary obstruction of the blood flow to the intestinal tract(3) would serve as an excellent test for this thesis. In particular, the reported ability of antibiotics(1,4) to afford protection by circumventing the usual intestinal bacteremia, required investigation in this type of shock.

Experiments in the rat reported herein do not support the concept of a systemic bacterial endotoxemia in bowel occlusion shock, but point rather to local factors within the intestine proper as the decisive elements in the fatal course of the syndrome.

Materials and methods. Two strains of rats, totaling 119 animals of both sexes, were used. These were German albino rats weighing 105 to 205 g and NAMRU stock rats weighing 110 to 300 g. In addition, 30 rats, which were excluded from the survival data, were used for observation of omental circulation, for measurements of mean arterial blood pressure, and for bacterial cultures. All rats were anesthetized with sodium pentobarbital (3 mg/100 g body weight, i.m.).

Shock was induced by temporary occlusion of the circulation to the intestinal tract. A midabdominal incision was made through the *linea alba* to minimize bleeding and the superior mesenteric artery was isolated. The artery was occluded with a wire serrafine clamp for 2 hours, and then released. The wound was closed and the rat returned to its cage. Aseptic precautions were taken throughout. Only those animals which survived the procedure are included in the data. Survival statistics are based on a 24-hour period of observation. Autopsies were performed routinely.

In representative members of each group of experimental animals, the blood was heparinized and mean arterial blood pressure was measured in the left carotid artery by a cannula leading to a conventional mercury manometer. Circulation of the omentum was also observed in these animals using Zweifach's visualization technic(5). Bacterial cultures (aerobic and anaerobic) were made on liver, spleen, intestine, and cardiac blood on selected animals (Table II).

Three series of experiments were conducted. In the first series, 6 groups of rats (77 animals) were given antibiotics. Five different antibiotics were employed, to pro-