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VASCULAR RESPONSES OF THE SPLEEN TO RAPID HAEMORRHAGE IN THE ANAESTHETIZED CAT

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SUMMARY

1. Splenic blood flow, splenic weight and arterial pressure were recorded in cats anaesthetized with sodium pentobarbitone. The mechanisms of the splenic contraction and vasoconstriction which followed rapid haemorrhage were investigated.

2. When splenic arterial pressure was decreased progressively by mechanical occlusion of the coeliac artery, the decrease in splenic blood flow was proportional to the decrease in pressure; splenic weight did not change.

3. After denervation of the spleen and adrenalectomy, haemorrhage resulted in a decrease in splenic flow which was similar to but slower than that in the innervated spleen; there was no splenic contraction. After splenic denervation, adrenalectomy and nephrectomy, haemorrhage caused a smaller decrease in flow but this response was still greater than that expected as a consequence of the reduced arterial pressure.

4. Infusions of small doses of angiotensin caused splenic vasoconstriction with little change in splenic weight. Larger doses reduced both flow and weight.

5. The splenic flow and weight responses to stimulation of the sympathetic nerves remained unimpaired when splenic blood flow was substantially reduced for 1–2 hr by haemorrhage.

6. It is concluded that after a rapid haemorrhage, the splenic contraction is due only to activity of the splenic nerves and the adrenal medullae. The decrease in splenic flow is due to the reduction in arterial pressure, activity of the splenic nerves and the adrenal medullae, and the actions of angiotensin and some unidentified vasoconstrictor substance.

INTRODUCTION

It is generally accepted that in cats and dogs the spleen contracts and its blood flow decreases following haemorrhage. Barcroft, Harris, Orahovats & Weiss (1925) estimated splenic volume from radiographs after marking the spleen with metallic sutures. They suggested that after small haemorrhages, a similar volume of blood to that removed was rapidly added to the circulation from the spleen. Lewis, Werle & Wiggers (1942) recorded splenic size by planimetry in dogs and reported a marked contraction following haemorrhage. Grindlay, Herrick & Mann (1939) observed a decrease in splenic blood flow following haemorrhage in dogs and this was maintained until retransfusion.

In analyses of the mechanisms of the vascular responses to haemorrhage, the factors which must be considered include the reduction in arterial pressure, reflex activation of the sympathetic nerves, discharge of catecholamines from the adrenal medullae, circulating angiotensin and accumulation of metabolites due to poor vascular perfusion. Although it is generally accepted that the splenic nerves play a predominant role, a quantitative analysis has never been described and recent papers on this subject by Zetterström, Palmerio & Fine (1964), Dahlström & Zetterström (1965) and Pinardi (1968) can be criticized (see Discussion). This paper describes the responses of the cat spleen to rapid haemorrhage and the roles of various mechanisms which play a part.

METHODS

Fifty-two cats (2–4 kg body weight) were anaesthetized by intraperitoneal injection of sodium pentobarbitone (Nembutal, 30 mg/kg, Abbott). When reflex limb and ear movements returned, additional doses of 8 mg sodium pentobarbitone were given through a cannula in a forelimb vein. Details of the methods used to record splenic and femoral arterial pressures and splenic flow and weight have been described (Greenway, Lawson & Stark, 1968). Briefly, splenic arterial blood flow was measured by a Nycotron electromagnetic flowmeter with a non-cannulating probe while the spleen lay on a cradle suspended from a strain gauge transducer. The flowmeter probe was attached to a micrometer-controlled artery clamp which could be tightened to reduce splenic arterial flow and pressure. The pressures, flows and weights during the control periods lay within the ranges previously described.

In forty-three experiments, the relationships of splenic flow and weight to arterial pressure were investigated. After a control period, splenic arterial pressure was reduced in approximately 20 mm Hg steps at 2 min intervals by means of the artery clamp. Pressure–flow and pressure–weight graphs were plotted for each animal.

The flow probe was positioned on the coeliac artery proximal to the point at which the splenic nerves joined the artery in order to avoid damage to these nerves. In some experiments the splenic nerves were divided and the peripheral ends were placed in a ring electrode connected to a Grass SD 5 stimulator. When it was important to obtain complete denervation, all connective tissue around the artery was cut

and cotton-wool soaked in 1 % lignocaine HCl (Astra-Hewlett) was placed around it. When required, the adrenal glands were removed and hydrocortisone (5 mg/kg, Upjohn Co.) was administered by intramuscular injection. In some animals, the kidneys were removed after ligation of the renal vessels and ureters.

Haemorrhage was induced by connecting a cannula in a femoral artery to a glass syringe containing 2 mg heparin (300 u. Boots). The arterial pressure was reduced to 50 mm Hg by removing blood at a mean rate of 14 ml. min^{-1} kg^{-1}. A further small volume was removed to maintain this pressure for 1 min. Thereafter no more blood was removed and arterial pressure was allowed to recover. The blood was stored at 38° C and reinfused intravenously after 30 min. In those experiments in which splenic arterial pressure, flow and weight returned to the pre-haemorrhage levels, a second haemorrhage was induced 1 hr later. In four cats, one haemorrhage was induced and the blood re-infused after 90 min.

Angiotensin (Hypertensin, Ciba) was dissolved in 0·9 % sodium chloride solution (w/v) and infused intravenously by a constant rate infusion pump.

RESULTS

Pressure–flow and pressure–weight graphs

In order to assess the role of the reduction in arterial pressure in the response to haemorrhage, the effects of local reduction in splenic arterial pressure were studied. Pressure–flow and pressure–weight graphs were obtained before section of the splenic nerves (fourteen cats), after section (twenty-five cats) and during stimulation at a frequency of 1 impulse/sec, 1 msec duration, 15 V (four cats). Three experiments from each group, selected by random numbers, are shown in Fig. 1. A near-linear relationship between pressure and flow was seen under all of these conditions and the splenic arterial bed showed little autoregulation of flow. Splenic weight did not vary as arterial pressure decreased. No attempt was made to study the change in slope produced by denervation or nerve stimulation in each animal but, since all the graphs were almost linear, the validity of the later calculations is established.

Responses to haemorrhage

Group 1: innervated spleen. The responses to sixteen haemorrhages were studied in eight cats in which the splenic nerves, adrenal glands and kidneys were intact. Blood was removed at a rate of $15 \pm 1{\cdot}7$ ml. min^{-1} kg^{-1} (mean ± S.E.) and the arterial pressure was reduced from $145 \pm 5{\cdot}4$ mm Hg to $52 \pm 2{\cdot}3$ mm Hg and maintained there for 1 min. The total volume removed was $70 \pm 4{\cdot}6$ ml. ($21 \pm 1{\cdot}3$ ml./kg). Splenic flow decreased from 53 ± 10 to $1{\cdot}9 \pm 1{\cdot}1$ ml./min and splenic weight from $46 \pm 2{\cdot}5$ to $30 \pm 1{\cdot}9$ g. Twenty minutes after the haemorrhage, the arterial pressure had recovered to 101 ± 11 mm Hg while the splenic flow was $7{\cdot}0 \pm 4{\cdot}5$ ml./min and the splenic weight was $31 \pm 3{\cdot}5$ g.

A typical experiment is shown in Fig. 2. Since the pressure–flow and pressure–weight graphs had been obtained before the haemorrhage, it was possible to calculate the flows and weights which would be expected from the local decrease in splenic arterial pressure after the haemorrhage. The interrupted lines in Fig. 2 show the results of such calculations. These

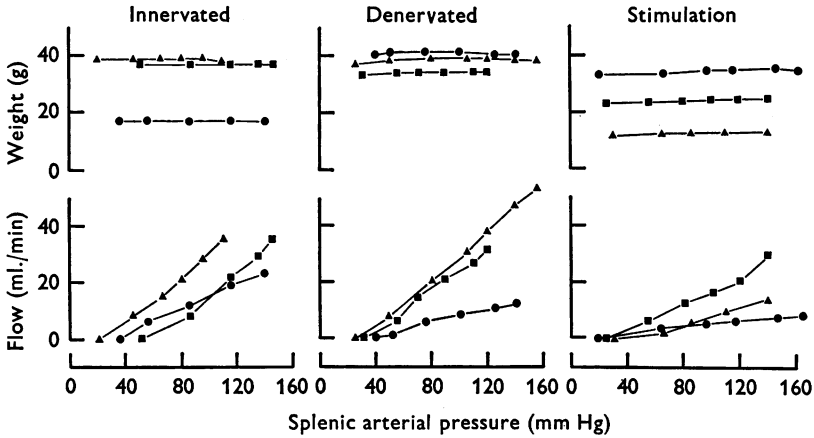

Fig. 1. Examples of pressure–flow and pressure–weight graphs from innervated spleens, denervated spleens and during stimulation of the splenic nerves at 1 impulse/sec.

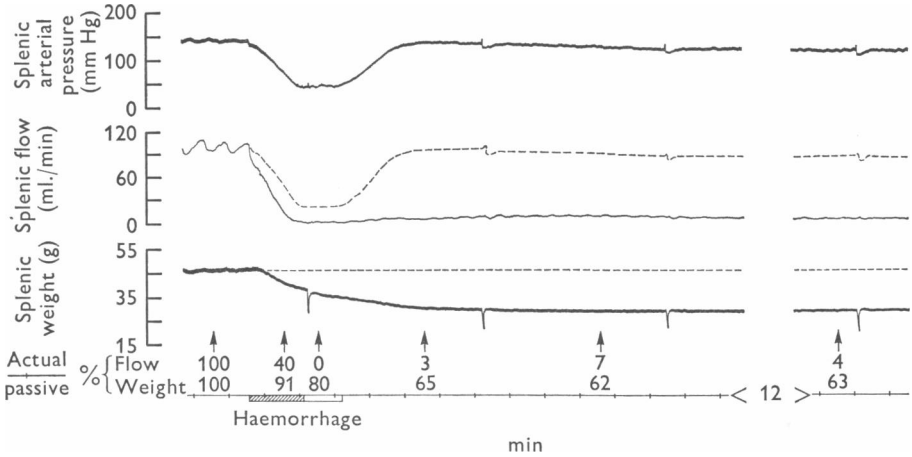

Fig. 2. Cat wt. 3·5 kg. The response to a haemorrhage (93 ml.) which reduced arterial pressure to 50 mm Hg (hatched bar) and held pressure at that level for 1 min (open bar). Ordinates, splenic arterial pressure, splenic flow and weight. Abscissa, time in min. The interrupted lines represent the passive flow and weight changes due to the decrease in splenic arterial pressure calculated from the pressure–flow and pressure–weight graphs. The ratios (as %) of actual to passive values for flow and weight are shown.

interrupted lines therefore represent the passive local response of the vascular bed to haemorrhage and since the actual responses deviate substantially from these lines, other extrinsic factors causing splenic contraction and vasoconstriction must be involved. To study these extrinsic factors, the actual flows and weights after the haemorrhage were expressed as percentages of the passive changes (Fig. 2). Thus, the extent of the deviation from 100 % represents the extent to which the flow and weight

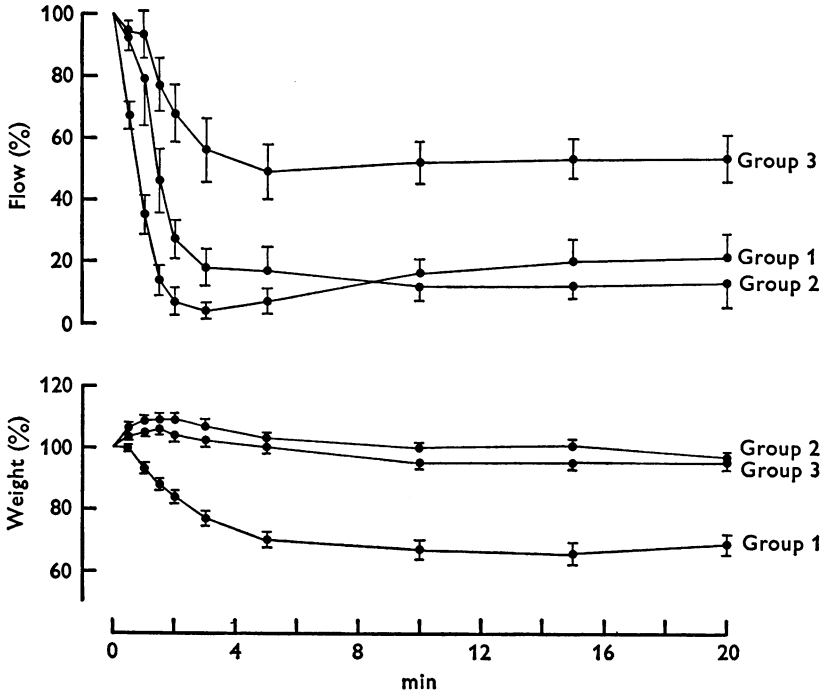

Fig. 3. The means and S.E. of the flow and weight responses following haemorrhage expressed as percentages of the values expected from the pressure–flow and pressure–weight graphs in the intact cats (Group 1), after splenic denervation and adrenalectomy (Group 2) and after splenic denervation, adrenalectomy and nephrectomy (Group 3).

were altered by extrinsic factors. This means of expressing the results permits comparison of the flow and weight responses in the different groups of cats. Figure 3 shows the means ($\pm$ S.E.) of the values in all the cats and it can be seen that marked vasoconstriction and contraction of the spleen due to extrinsic factors occurred in the cats with innervated spleens and intact adrenal glands (Group 1).

When the splenic flow and weight had returned to the pre-haemorrhage levels after reinfusion of the blood, the splenic nerves were divided and

stimulated at a frequency of 3 impulses/sec (1 msec, 15 V), which produces a maximal weight response (Greenway *et al.* 1968). The weight loss following the haemorrhage was $61 \pm 4{\cdot}9\,\%$ of the weight loss in response to this stimulation of the splenic nerves.

Group 2: splenic denervation and adrenalectomy. Eleven haemorrhages were induced in seven cats after denervation of the spleen and adrenalectomy. Blood was removed at the rate of $14 \pm 1{\cdot}8$ ml. min^{-1} kg^{-1} and the arterial pressure was reduced to $50 \pm 1{\cdot}8$ mm Hg and maintained there for 1 min. The total volume removed was $42 \pm 4{\cdot}0$ ml. ($14 \pm 1{\cdot}5$ ml./kg). This is significantly less than the amount removed in Group 1 (see Discussion) but the rate of removal was similar. After 20 min the arterial pressure had recovered to $91 \pm 5{\cdot}3$ mm Hg. The flow response was similar to that obtained in the innervated spleen but it developed more slowly (Group 2, Fig. 3). No splenic contraction occurred and there was usually a small initial relaxation.

In three cats in which only the splenic weight was recorded, the responses to haemorrhage before and after section of the splenic nerves were compared. The adrenal glands were intact. Following haemorrhage the splenic weight decreased to $72 \pm 6{\cdot}7\,\%$ of the pre-haemorrhage value before and to $85 \pm 7{\cdot}1\,\%$ after denervation. These findings suggest that both the splenic nerves and the secretions of the adrenal medulla cause contraction of the spleen after rapid haemorrhage.

Group 3: splenic denervation, adrenalectomy and nephrectomy. Eight haemorrhages were induced in four cats after denervation of the spleen, adrenalectomy and nephrectomy. Blood was removed at the rate of $13{\cdot}5 \pm 1{\cdot}8$ ml. min^{-1} kg^{-1} and the arterial pressure was reduced to $49 \pm 1{\cdot}6$ mm Hg and maintained there for 1 min. The total volume removed was $34 \pm 4{\cdot}5$ ml. ($12 \pm 1{\cdot}7$ ml./kg). After 20 min the arterial pressure had recovered to $102 \pm 4{\cdot}7$ mm Hg. The decrease in blood flow was less than in Groups 1 and 2 and it occurred more slowly than in these groups. However the flow still decreased to 50 % of the value expected from the pressure–flow graphs (Group 3, Fig. 3) suggesting that some additional factor was causing vasoconstriction. As in Group 2, the spleen relaxed slightly after the haemorrhage.

Infusions of angiotensin

In three female cats, angiotensin (0·06–1·0 μg/min) was infused intravenously. Arterial pressure usually increased during the infusions but the pressure in the splenic artery was maintained constant with the artery clamp. Figure 4 shows a typical series of responses to angiotensin. At low infusion rates, flow decreased but there was no change in splenic weight. At higher rates of infusion, the flow response was greater and weight decreased. There was often a brief increase in blood flow to above the pre-

infusion level shortly after the initial flow decrease. The cause of this is not known.

Stimulation of the splenic nerves

The purpose of this group of experiments was to examine whether the responses to stimulation of the splenic nerves were impaired when the splenic blood flow was reduced for prolonged periods by haemorrhage or by complete occlusion of the splenic artery.

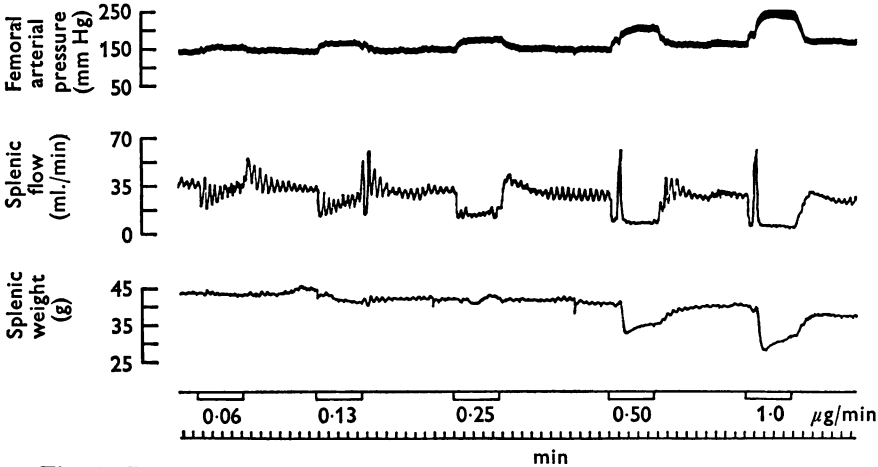

Fig. 4. Cat wt. 3·2 kg. The responses to infusions of angiotensin. Ordinates, femoral arterial pressure, splenic flow and weight. Abscissa, time in min. Angiotensin was infused intravenously during the periods shown. The splenic arterial pressure was kept constant during each infusion.

In four cats with intact adrenal glands and kidneys, the splenic nerves were cut and prepared for stimulation. Splenic arterial flow was reduced to and maintained at one third of the control level for periods of 70–90 min. To do this, it was necessary to remove blood at first rapidly and then more slowly and the total volume of blood removed was $10 \pm 3{\cdot}6$ ml./kg. At 15 min intervals during this time, the splenic nerves were stimulated at 2–3 impulses/sec (1 msec, 15 V). The last response differed from the first response by 0–25% (mean 5%) in the case of splenic flow and 17–21% (mean 19%) in the case of splenic weight. Thus the responses to stimulation of the splenic nerves were not altered by 90 min periods of reduced flow whether this was produced mechanically (Greenway *et al.* 1968) or by haemorrhage.

In five cats, the ability of the spleen to contract after periods of complete cessation of flow was investigated. In each experiment a control response to stimulation of the splenic nerves (3 impulses/sec, 1 msec, 15 V) was first obtained during normal blood flow. The splenic artery was occluded for

2–60 min and the nerves were then stimulated for 2 min. Since the artery remained occluded during stimulation, flow was zero but the change in splenic weight was recorded. After 2 min of splenic arterial occlusion, the weight responses were reduced by 0–25 % (mean 13 %) of the control, after 18 min by 0–25 % (mean 16 %) and after 60 min by 0–17 % (mean 9 %). Thus even complete occlusion of the splenic artery for up to 60 min did not reduce the splenic contraction in response to sympathetic nerve stimulation.

DISCUSSION

Pressure–flow relationships in the dog spleen have been described previously (Frohlich & Gillenwater, 1963). An approximately linear relationship between pressure and flow was observed and no evidence of active myogenic responses was obtained. However, in these experiments, the arterial supply to the spleen was long-circuited through a pump and such long-circuits are well known to alter vascular reactivity (Folkow, 1953) and to modify or abolish pressure-induced autoregulation (Green, Rapela & Conrad, 1963). These objections do not apply in our experiments since no arterial long-circuits were used. The approximately linear pressure–flow relationship in the splenic vascular bed is in marked contrast to the autoregulation seen in other abdominal vascular beds such as intestine (Johnson, 1960), liver (Greenway, Lawson & Mellander, 1967) and kidney (Folkow & Langston, 1964). This is perhaps surprising since large oscillations in flow are seen which appear to be caused by myogenic rhythmic activity in the splenic resistance vessels (discussed by Greenway *et al.* 1968). Splenic weight did not change when arterial pressure was reduced. The smooth muscle of the splenic capsule and trabeculae does not appear to show either pressure-induced myogenic contractions or passive responses to changes in arterial pressure.

Haemorrhages in different experiments may be compared either by removing similar volumes of blood or by producing similar degrees of hypotension. In Group 1 (innervated spleen), the spleen contracted and added approximately 16 ml. to the circulating blood volume while in Groups 2 (denervated spleen and adrenalectomy) and 3 (denervated spleen, adrenalectomy and nephrectomy) this did not happen. Also the surgical procedures were more extensive in Groups 2 and 3. It did not appear reasonable to remove equal volumes of blood from the three groups of cats and therefore blood was removed at a constant rate until comparable degrees of hypotension were produced. The large difference in the volume of blood removed between Group 1 and Groups 2 and 3 is largely accounted for by the splenic contraction in Group 1.

Following rapid haemorrhage, the splenic vasoconstriction and con-

traction were maintained with little recovery over 30 min. This is consistent with our observations that the response to stimulation of the sympathetic nerves shows little progressive impairment when the flow is reduced by local mechanical obstruction or by haemorrhage. This is in contrast to the marked progressive impairment of the response in the vascular beds of skeletal muscle (Lewis & Mellander, 1962; Mellander & Lewis, 1963; Rothe, Schwendenmann & Selkurt, 1963) and intestine (Folkow, Lewis, Lundgren, Mellander & Wallentin, 1964). The ability of the splenic smooth muscle to respond to sympathetic nerve stimulation for long periods after occlusion of the arterial supply may be due to some inherent resistance to anoxia. However, the spleen contains concentrated red cells and may possess a reserve of oxygen. Whatever the mechanism, the ability to maintain both vasoconstriction and contraction for long periods despite a negligible blood flow is of functional significance after a haemorrhage in the cat. Contraction increased the blood volume by $4{\cdot}5 \pm 0{\cdot}4$ ml./kg and this is approximately 9 % of the normal blood volume (Groom, Rowlands & Thomas, 1965). The splenic fraction of the cardiac output, which is approximately 7 % in the cat (Greenway *et al.* 1968), was diverted to other more vital organs.

The contraction following haemorrhage was 61 % of that produced by maximal stimulation of the sympathetic nerves. From the frequency–response curves (Greenway *et al.* 1968), this corresponds to a mean frequency in all the splenic nerve fibres of 1 impulse/sec. This figure must be regarded as approximate but it is considerably lower than that for the sympathetic nerves to skeletal muscle blood vessels after haemorrhage, calculated by a similar method (Lundgren, Lundwall & Mellander, 1964).

Our experiments confirm that splenic contraction does not occur after both denervation of the spleen and adrenalectomy. However, when the spleen was denervated but the adrenal glands left intact, a smaller but still significant contraction of the spleen occurred. Thus in cats subjected to rapid haemorrhages of this magnitude, the adrenal medullary secretions can cause a significant contraction of the spleen. This is at variance with results obtained in the dog by Dahlström & Zetterström (1965), Zetterström *et al.* (1964) and Pinardi (1968). However, in their experiments the changes in volume of innervated and denervated portions of the spleen were inferred from the changes in length or by visual observation. In Pinardi's experiments, the first recording was made 30 min after the haemorrhage and the only statistically significant difference between the innervated and denervated portions occurred at some unstated time after this.

It was surprising that the splenic flow response following haemorrhage was hardly modified by denervation and adrenalectomy. The response

was somewhat slower but flow still decreased to very low levels. The fact that splenic weight did not change is evidence that the spleen was completely denervated and that no significant amounts of circulating catecholamines from other sources were present. Stimulation of the splenic nerves has never been shown to cause vasoconstriction without contraction and the smooth muscle of the capsule and trabeculae is at least as sensitive as that of the resistance vessels to both adrenaline and noradrenaline (Davies, Gamble & Withrington, 1968). Thus other extrinsic factors were causing vasoconstriction but not contraction of the spleen. Angiotensin is known to be secreted following a haemorrhage and in the dog, amounts up to 1·5 μg/min are formed (Regoli & Vane, 1966; Hodge, Lowe & Vane, 1966). Angiotensin has been reported to cause splenic vasoconstriction but not contraction (Boatman & Brody, 1964; Davies *et al.* 1968). Our experiments confirmed that, in small doses, angiotensin decreased splenic flow without changes in weight although, in larger doses, contractions did occur. Angiotensin may therefore be a cause of splenic vasoconstriction after haemorrhage and our observations that the decrease in splenic flow is significantly smaller after nephrectomy support this conclusion.

However, even after splenic denervation, adrenalectomy and nephrectomy, the decrease in splenic flow was significantly greater than that expected from the local effect of the decrease in arterial pressure. Clearly some other vasoconstrictor factor is involved and this factor has not been identified. It is not known whether the amounts of vasopressin secreted by the posterior pituitary after haemorrhage in the cat are sufficient to decrease splenic flow. Intravenous infusions of 8–16 mu./min cause a 50% decrease in splenic flow without contraction in the cat (C. V. Greenway & R. D. Stark, in preparation). It seems possible that vasopressin may be another cause of the splenic vasoconstriction after rapid haemorrhage.

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