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A STUDY OF GASTRIC SECRETION AND BLOOD FLOW IN THE ANAESTHETIZED DOG

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A number of authors have attempted to measure gastric blood flow and to relate this to the secretory activity of the gastric mucosa. These include Burton-Opitz (1910), Boenheim (1930*a*, *b*) and more recently, Willox, Michalyshyn & Kowalewski (1961), who directly measured venous outflow from the stomach of the anaesthetized dog. Herrick, Essex, Mann & Baldes (1934) used a thermostromuhr, placed around the mesenteric artery, to measure blood flow to the viscera. Measurements of blood flow and secretion in the viviperfused dog's stomach were made by Lim, Necheles & Ni (1927) and by Ni & Lim (1928). Secretory activity and venous outflow from the stomach were measured in the anaesthetized cat by Cutting, Dodds, Noble & Williams (1937), and Thompson & Vane (1953) related secretory activity and blood flow in the perfused stomach of the cat. The results obtained by the above authors differ, and Thompson & Vane are alone in stating that gastric secretory activity is directly related to gastric blood flow.

It was decided to investigate the relation between secretion and blood flow in anaesthetized dogs by a technique based on that of Burton-Opitz (1910).

METHODS

Animals. Healthy mongrel dogs (6·0–22·0 kg body weight) were used. Food was withheld for 24 hr before the experiment, but the animals were allowed water *ad lib.*

Operative procedure. Anaesthesia was induced by Na pentobarbitone I.V. (30–40 mg/kg body wt.) and maintained by further small doses (6–60 mg) given as required during the experiment. The technique, which has been described briefly in a previous communication (Cumming, Haigh, Harries & Nutt, 1961), was developed after dissection of the venous system in several dye-perfused specimens. These showed that it was possible to collect the whole of the gastric venous drainage without removal of the intestine.

The abdomen was opened through a mid-line incision, the spleen removed close to the hilum, and the greater omentum excised, preserving the vasa brevia. That part of the pancreas which invests the splenic vessels was next dissected free and its vascular connexions with the splenic artery and vein ligated. The junction of the splenic and superior mesenteric veins was exposed beneath a large lymph node. Veins from the lymph node enter the major

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vessels at this point and were tied before a ligature was placed around the splenic vein, as close to its junction with the superior mesenteric vein as possible. The pylorus was tied with cotton tape and the right gastro-epiploic vein included in the ligature to prevent any gastric venous blood from passing into the portal vein. A plastic stomach tube (external diameter 6 mm) was next passed into the stomach, through the mouth, and held in place by a tape securing it to the lower jaw.

A femoral artery and vein were prepared for cannulation, as was one external jugular vein and one cephalic vein. After all operative procedures were completed the animal was allowed to rest for 1 hr in order that it might recover from the effects of the operation and to allow haemostasis of the wounds to occur.

The animal was then given 50 mg heparin in 2 ml. NaCl solution (0·9 g/100 ml.) intravenously and cannulae were inserted as follows:

(1) A glass cannula connected to a mercury manometer was used to record blood pressure from the femoral artery.

(2) A double polythene cannula was inserted into the cephalic vein for the infusion of NaCl solution (0·9 g/100 ml.) and Na pentobarbitone solution.

(3) A triple polythene cannula was inserted into the jugular vein for the infusion of histamine, adrenaline and noradrenaline as required.

(4) The cannula through which the venous outflow from the stomach returned from a flowmeter was inserted into the femoral vein, the flowmeter and its connexions having been filled with NaCl solution (0·9 g/100 ml.).

(5) Two cannulae which delivered blood to the flowmeter were inserted into the length of the splenic vein in such a way that, when its junction with the mesenteric vein was tied, they collected the entire gastric venous outflow.

Flowmeter. An automatically recording closed-circuit bubble flowmeter was used to measure the gastric venous outflow. The apparatus has been described fully in a previous communication (Haigh & Sandland, 1961).

Collection of gastric juice. Gastric contents were collected by means of an open-ended plastic tube, external diameter 6 mm, with perforations in its terminal 12 cm. The tube was introduced orally, as described above, and extended along about two-thirds of the greater curvature of the stomach. Aspiration of gastric contents was achieved by intermittent suction (pressure 40–50 mm Hg). A continuous current of air was blown through a fine polythene tube, external diameter 1 mm, which lay within the stomach tube and protruded at its tip. This, by inflating the stomach slightly, prevented mucosal damage and occlusion of the holes in the stomach tube. Care was taken to avoid over-distension of the stomach with air.

Gastric samples were collected directly into 15 ml. graduated tubes and their volume recorded. Free and total acidity were determined by electrometric titration of 1 ml. samples with N/100 NaOH to pH 3·5 and 8·0 respectively. After collection of each sample of gastric juice NaCl solution (0·9 g/100 ml.) equal to it in volume was infused through the cannula in the cephalic vein.

Constant infusion of drugs. Drugs were infused through the external jugular vein by means of a constant-rate injection apparatus. Histamine acid phosphate 2·5–10·0 μg/kg/min, and adrenaline or noradrenaline 1·0–8·0 μg/kg/min were infused as required.

Antihistamine treatment. Six animals were given mepyramine maleate 2·0 mg/kg intramuscularly 30 min before starting the infusion of histamine.

RESULTS

Total body weight and stomach weight. Thirty-five dogs were used for these measurements. The mean total body weight of the series was 12·3 kg, (S.D. 0·88) and the mean stomach weight 122 g, (S.D. 33·2). The stomach

weight represents a mean of 1·0 % of the total body weight (S.E. of mean 0·2 %). This ratio of stomach weight to body weight was similar in the 19 male and 16 female dogs studied.

Gastric blood flow under basal conditions. Thirty-five experiments were performed where blood flow through the stomach was measured under basal conditions. Immediately after cannulation of the veins draining the stomach there was a period of rapid blood flow, which never lasted more than 10 min, and which we presumed to be due to reactive hyperaemia. A steady rate of blood flow was then obtained, the mean rate being 14·0 ml./100 g wet tissue/min (S.E. of mean 1·0). The mean systemic arterial pressure during these measurements was 120 mm Hg (S.E. of mean 3·4).

Effect of histamine on gastric blood flow and systemic arterial pressure. Intravenous infusions of histamine acid phosphate (10·0, 5·0 or 2·5 μg/kg/min) were given to 30 dogs; 6 of these animals received mepyramine maleate before the infusion.

Two dogs received 10·0 μg doses of histamine. Gastric blood flow rose by 10 and 40 % in these animals, though systemic arterial pressure fell from 100 to 65 mm Hg and from 125 to 85 mm Hg respectively.

Eight animals were given histamine 5·0 μg/kg/min. The mean arterial pressure before infusion was 126 mm Hg (S.E. of mean 9·2) and this fell to a 'plateau' of 89 mm Hg (S.E. of mean 17·3) within 30 min. Within 2–3 min of beginning the histamine infusion, blood flow fell slightly in 4 animals, rose slightly in 3 and markedly in 1 animal in which the basal rate had been low (5·9 ml./100 g wet weight of stomach/min). After 30 min a steady rate of flow was reached which was lower than the basal rate in 6 of the animals and higher in two of them. Mean rates for the group showed no significant change either immediately or 30 min after starting the infusion. The mean basal rate of flow was 14·2 ml./100 g/min (S.E. of mean 2·0). Immediately after histamine infusion the mean rate was 14·2 ml./100 g/min (S.E. of mean 2·6) and 30 min later, during the steady state, was 14·3 ml./100 g/min (S.E. of mean 2·7).

Twenty dogs received histamine 2·5 μg/kg/min; these included the six which were given mepyramine maleate (2·0 mg/kg) 30 min before starting the infusion of histamine. Mean systemic arterial pressure in the 14 animals without anti-histamine was 126 mm Hg (S.E. of mean 3·8). This fell to 97 mm Hg (S.E. of mean 5·3) after 30 min of histamine infusion. In the 6 animals which were given anti-histamine systemic arterial pressure fell to a mean of 100 mm Hg (S.E. of mean 9·0) as a result of this. On giving histamine arterial pressure fell further to a mean of 82 mm Hg (S.E. of mean 9·0), a value somewhat lower than that in animals given histamine alone. Effects on stomach blood flow in these 20 animals were similar to those in animals given histamine 5·0 μg/kg/min. The mean basal

rate of flow was 14·3 ml./100 g stomach/min (S.E. of mean 1·7). This rose slightly to a mean rate of 15·6 ml./100 g stomach/min (S.E. of mean 2·3) within 2–3 min of the beginning of the infusion, representing a slight fall in rate in 12 animals and a rise in 7; in 1 animal the rate of flow was unchanged. After 30 min the mean rate was 16·3 ml./100 g stomach/min (S.E. of mean 1·4), having fallen slightly in 6 animals and risen slightly in 12; in 2 cases the rate of flow did not change. The rise in the mean rate of flow 30 min after beginning the infusion of histamine is not statistically significant. It was, however, noted that in those animals which showed a rise in rate of gastric blood flow 30 min after beginning the histamine infusion the rise was coincident with the onset of acid secretion by the stomach.

Results in animals given mepyramine maleate did not differ from those in dogs given histamine alone.

In many of the experiments, with all doses of histamine, small cyclical changes in blood flow occurred. These appeared to coincide with gastric peristalsis.

TABLE 1. Secretory response (total acid) to different I.V. infusions of histamine acid phosphate

Number of dogs	Dose of histamine acid phosphate (μg/kg/min)	Secretory response (mean and range: total acid, m-equiv/min)
16	2·5	0·041 (0·01–0·11)
9	5·0	0·078 (0·01–0·25)
2	10·0	0·03 and 0·18

Effect of histamine on gastric secretion. In 27 of the above 30 animals a sustained secretion of acid was obtained in response to the infusion of histamine. The responses obtained were variable and are summarized in Table 1. It will be seen that the mean rate of secretion in the groups of animals receiving histamine acid phosphate 2·5 or 5·0 μg/kg/min is related to the dose. There was no statistically significant relation between stomach blood flow and the rate or occurrence of acid secretion. Acid secretion was not maintained when the arterial pressure fell below 60 mm Hg.

Action of adrenaline on gastric blood flow and histamine-induced secretion. L-Adrenaline tartrate was given by continuous intravenous infusion (1·0, 2·0, 4·0 or 8·0 μg/kg/min) for at least 30 min, in 23 experiments, during the period of histamine-induced acid secretion. In 19 of these experiments it was given as a first or only infusion, and in the other 4 animals it followed infusions of noradrenaline.

The mean rate of blood flow before giving adrenaline was 18·0 ml./100 g/min (range 5·5–64·0 ml.). On infusing adrenaline there was, in all but two cases, an immediate increase in blood flow which reached a maximum rate

within 2–3 min. With doses of 1·0 and 2·0 μg of adrenaline the rate remained constant so long as the infusion continued. With 4·0 and 8·0 μg doses blood flow increased to a peak value within 2–3 min and then decreased slightly to reach a constant, but increased, rate within 5–10 min. This constant rate was then maintained until the end of the infusion. The mean constant rate of blood flow at all doses of adrenaline was 37·8 ml./100 g/min (range 9·9–77·5 ml.), an increase which is highly significant ($P < 0{\cdot}001$). These results include those in one animal given 1·0 μg adrenaline/kg/min, where blood flow and arterial pressure fell slightly, and in one given a 4·0 μg infusion, where flow remained constant while arterial pressure fell slightly.

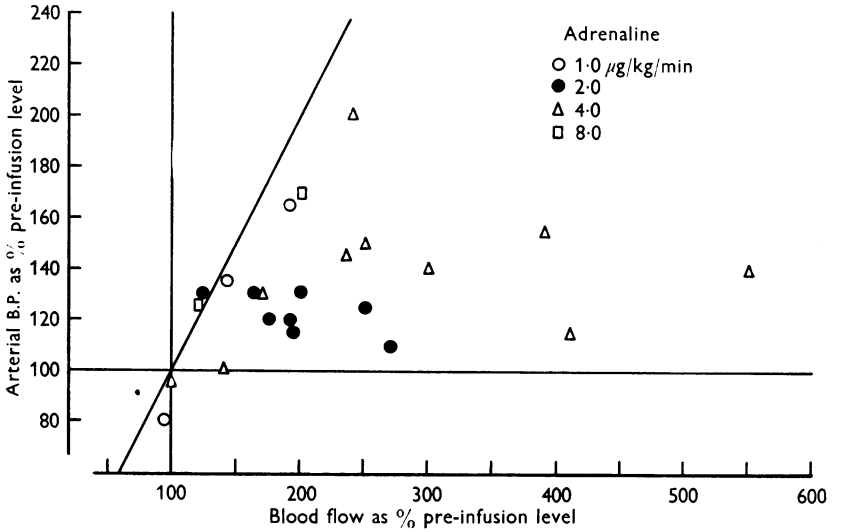

Fig. 1. The changes occurring in systemic arterial blood pressure and total gastric blood flow during intravenous infusion of adrenaline (percentage of the pre-infusion level).

Changes in systemic arterial pressure followed a similar time course to changes in gastric blood flow. Mean pressure before the infusion of adrenaline was 89 mm Hg (range 60–130 mm) and the mean steady level during the infusion of adrenaline was 117 mm Hg (range 55–185 mm).

Figure 1 summarizes the effects of different doses of adrenaline on gastric blood flow in relation to systemic arterial pressure. Blood flow and arterial pressure are expressed as percentages of their values immediately before the start of the adrenaline infusion. Neither the change in rate of flow nor in arterial pressure is very closely related to the dose of adrenaline given. Individual animals showed widely differing sensitivity to its circulatory effects. The solid line in the figure indicates the increase in

blood flow to be expected if this were due solely to increase in perfusion pressure. In all but two cases, including those in which blood pressure and flow decreased, the points plotted lie to the right of this theoretical line, thus indicating a decrease in peripheral resistance due to vasodilatation in the stomach. In two cases the increased blood flow seems to be accompanied by some slight degree of gastric vasoconstriction.

In the 19 experiments where adrenaline was given as the first infusion in addition to histamine its effect on the rate of acid production by the stomach was very variable. The rate of secretion increased in 9 animals, decreased in 6, and was unchanged in 4.

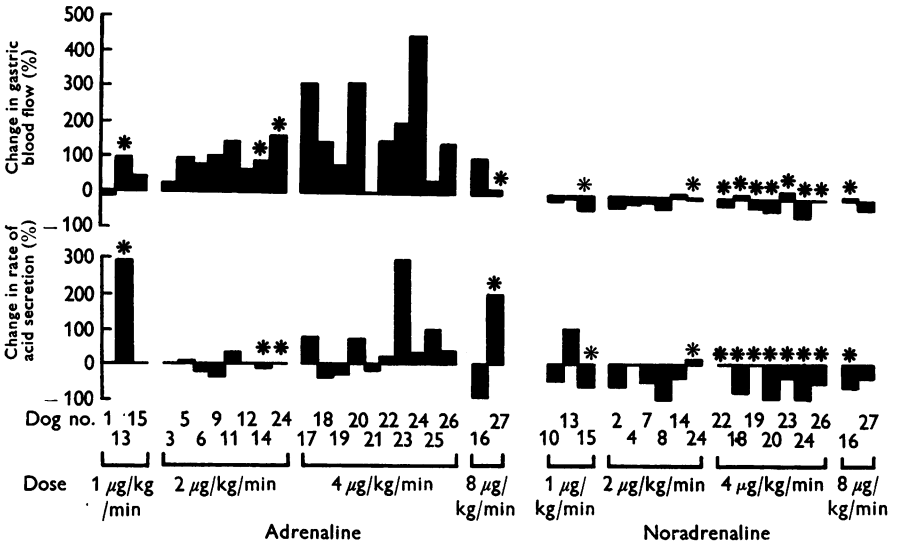

Fig. 2. Comparison of the effect upon histamine-induced gastric acid secretion and total gastric blood flow of intravenous infusions of adrenaline and noradrenaline.

* Indicates that an infusion of the other catechol amine had been given some time previously.

Figure 2 summarizes the effects of continuous infusion of adrenaline on both blood flow and gastric acid secretion in all 23 experiments. The animals which received adrenaline as a second infusion, having previously been given a similar dose of noradrenaline, are indicated by asterisks. Rates of blood flow and secretion are recorded as percentages of their value before the adrenaline infusion. There seems to be no relation between changes in blood flow and changes in rate of secretion, and the variation in the results is so great that it is impossible to predict the effect of adrenaline on the secretory activity of the stomach. On stopping the infusion of adrenaline, systemic arterial blood pressure and gastric blood flow returned to the pre-infusion levels, or slightly below these values, within 2–3 min. Inhi-

bitory effects on secretory activity persisted for at least 30 min longer, whereas stimulatory effects ceased almost as abruptly as the circulatory effects.

Action of noradrenaline on gastric blood flow and histamine-induced secretion. L-noradrenaline tartrate was given (1·0, 2·0, 4·0 or 8·0 μg/kg/min) by continuous intravenous infusion, for at least 30 min in 18 experiments. In 8 of these it was given as a first or only infusion and in 10 it followed an infusion of adrenaline. In animals where adrenaline had been given an interval of at least 30 min elapsed before the infusion of noradrenaline.

The mean rate of gastric blood flow before infusion of noradrenaline was 20·3 ml./100 g/min (range 9·8–48·0 ml.) and this decreased to a mean rate of 17·4 ml./100 g/min (range 8·4–37·2 ml.) within 2–3 min of starting the infusion. These results represent a decrease in flow in all but four animals, in which slight rises of 0·1, 0·8, 1·6 and 2·8 ml./100 g/min occurred. The magnitude of the change in flow was less than with similar doses of adrenaline, but the decrease is statistically significant ($P < 0·01$). Blood flow continued at the decreased rate throughout the infusion of noradrenaline.

The mean level of systemic arterial blood pressure before infusion of noradrenaline was 84 mm Hg (range 50–115 mm) and the mean steady level during the infusion increased to 108 mm Hg (range 75–150 mm).

Figure 3 shows the changes in gastric blood flow in relation to changes in systemic arterial pressure during the infusion of different doses of noradrenaline. As in the case of adrenaline infusion, the magnitude of the changes, which are plotted as percentages of the pre-infusion values, is not closely related to dose. With noradrenaline all the points lie to the left of the theoretical line of direct proportionality between changes in blood flow and perfusion pressure. Decrease in gastric blood flow was thus the result of increased peripheral resistance. In those cases where blood flow did increase slightly in rate this was due to increase in perfusion pressure overcoming the vasoconstrictor effects of the noradrenaline on the gastric vessels.

In these 18 experiments a satisfactory level of acid secretion (mean rate 0·052 m-equiv/min) was obtained before the infusion of noradrenaline. In 13 of these experiments the rate of acid secretion decreased in response to noradrenaline, in 2 it rose and in 3 it remained unaltered. The mean rate of secretion during noradrenaline infusion was 0·024 m-equiv/min. The decrease in acid secretion which occurred was statistically significant ($P = 0·01$).

Figure 2 also summarizes the effects of noradrenaline on gastric blood flow and histamine-induced acid secretion. Animals in which the noradrenaline infusion followed a similar dose of adrenaline are indicated by an asterisk.

As in the case of adrenaline, the circulatory effects disappeared rapidly on ceasing the infusion, whereas the inhibitory effects on gastric acid secretion persisted much longer, up to 2–3 hr in some cases.

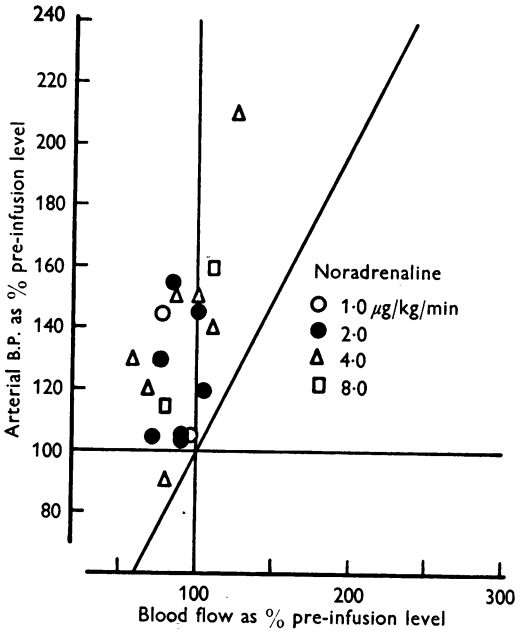

Fig. 3. The changes occurring in systemic arterial blood pressure and total gastric blood flow during intravenous infusions of noradrenaline (percentage of the pre-infusion level). The upper of the two overlapping circles (blood flow 90 %) should be open circle, representing 1·0 μg/kg/min.

DISCUSSION

The measurement of blood flow through the stomach was first accomplished, with limited success, by Burton-Opitz (1910). Later reports of blood-flow measurements include those of Lim *et al.* (1927), Ni & Lim (1928), Boenheim (1930*a*, *b*), Cutting *et al.* (1937), Thompson & Vane (1953) and Willox *et al.* (1961). All these workers attempted some form of direct measurement of flow, although Willox *et al.* (1961) combined their direct observations with measurements of temperature of the stomach mucosa in an attempt to obtain an index of local blood flow. Two groups of workers, Lim *et al.* and Thompson & Vane, used perfusion techniques, with a donor animal and a Dale–Schuster pump respectively. All the other workers made measurements of the gastric venous outflow.

Burton-Opitz's technique, which has formed the basis of all subsequent methods of venous outflow measurement, was limited to a small number of

observations per animal, obtained before the blood in his cannulae clotted. It is of interest to compare the results he obtained in the dog with those of subsequent workers, including those reported in this paper. Burton-Opitz obtained a mean stomach blood flow of 20·5 ml./100 g wet tissue/min with a mean systemic arterial pressure of 86 mm Hg.

Lim and his colleagues perfused transplanted stomachs or stomach pouches by anastomosing the coeliac artery and mesenteric vein with the carotid artery and external jugular vein of the donor animal. Metal couplers were used to join the vessels in such a way that the intimal surfaces only were in contact and anticoagulants were unnecessary. Both homoeo- and autoperfusion was carried out and the perfuser animal was unanaesthetized, anaesthetized or decerebrate. In some cases the stomach was removed from the animal and then reconnected to the original blood supply, thus ensuring the complete severance of nervous connexions. In these experiments the mean rate of blood flow under basal conditions was found to be 34 ml./100 g wet weight of stomach/min. The mean systemic arterial pressure, in those animals in which this was measured, was 100 mm Hg. These apparently high basal rates of flow may be due in part to the absence of nervous vasomotor control of the stomach vessels. It may also be due to the fact that the stomach of a small animal was usually perfused by anastomosis with the vessels of a larger donor animal.

Boenheim (1930*a*) used a method similar to that of Burton-Opitz, but the use of anticoagulants enabled measurements to be made for longer periods. He obtained a mean rate of flow of 26·5 ml./100 g wet weight of stomach/min, in spite of a low mean systemic arterial pressure of 60 mm Hg. This low blood pressure may be explained in part by the evisceration to which some of his animals had been subjected.

Willox *et al.* (1961) measured the outflow from the splenic vein of anaesthetized dogs by collecting the total venous effluent, via a system of cannulae, for 1 out of every 4 min. The blood so collected was then returned to the animal through a cannula in the femoral vein. Heparin was used as an anticoagulant. Unfortunately the left gastric vein from the lesser curve did not drain into the system, so that only a fraction of the venous outflow was measured. The weights of the animals' stomachs are not recorded, so that the rate of blood flow of 31 ml./min cannot be compared with that of other workers.

The work of Cutting *et al.* (1937) and of Thompson & Vane (1953) was carried out on cats. Neither of these groups of workers have given the stomach weights of their animals. Cutting *et al.* obtained rates of flow of 15–30 ml./min in anaesthetized cats, but these rates declined rapidly, along with systemic arterial pressure, probably again as the result of evisceration of the animals. Thompson & Vane perfused stomach preparations with

blood from a carotid artery carried via a polythene coil to enter the coeliac artery. In most of their experiments a Dale–Schuster pump and bubble flowmeter were included in the circuit. The authors have not recorded mean rates of flow in their report, but in one kymograph tracing provided they appear to have obtained a blood flow of 30 ml./min at a perfusion pressure of 145 mm Hg.

The rates of blood flow obtained in our present series of experiments (mean 14·0 ml./100 g/min) are low in comparison with those of earlier workers, being approximately 50% of the value obtained by Burton-Opitz. Possible explanations of this difference are that we took care to avoid damage to nerve fibres running with the blood vessels, and that improvements in anaesthetic and surgical technique since 1910 resulted in animals with a higher degree of nervous vasomotor control. This is supported by the finding that the mean systemic arterial pressure of our animals, even after 6–8 hr of anaesthesia, was higher than that recorded by earlier workers at the start of their experiments. Also, though it was never necessary to occlude the venous drainage completely during cannulation of the splenic vein, an initial period of rapid flow was observed in every case when recording began. This was presumed to be due to reactive hyperaemia. It seems likely that the more rapid rates of blood flow found by others could be accounted for by some degree of reactive hyperaemia. This is not improbable when it is realized that Burton-Opitz was obliged to occlude the venous drainage of the stomach for 10 min and could record blood flow for only a maximum period of 20 min thereafter.

It might be objected that by returning the blood in closed circuit to the femoral vein a vascular resistance different from that of the hepatic portal system was being employed. It was found, in our experiments, that the venous pressure at the stomach side of the flowmeter ranged from 5 to 10 cm blood, a value somewhat lower than that reported in the portal vein (12–13 cm H_2O, Best & Taylor, 1961). If we had maintained a higher vascular resistance to the gastric venous effluent, it is possible that the rates of resting blood flow would have been somewhat lower than those which we recorded.

Geber (1960) has suggested that heparin may have an effect on the rate of blood flow through the splanchnic bed. He showed that 10–20 mg, dissolved in NaCl solution (0·9 g/100 ml.) injected into branches of the coeliac artery, increased the rate of blood flow by 5–15% for up to 15 sec after injection. We have never observed the injection of 50 mg of heparin into the femoral vein to have any effect on the rate of blood flow from the stomach.

It has been possible to obtain good acid secretory responses, in anaesthetized animals which had undergone extensive operations, by the

intravenous infusion of much smaller doses of histamine than those often found necessary (Lim *et al.* 1927; Thompson & Vane, 1953), and comparable with those employed in unanaesthetized dogs (Forrest & Code, 1954; Harries, 1957). Most other workers have given large doses of histamine subcutaneously or intramuscularly, so that direct comparison of doses is difficult.

The observation in some of the present series of experiments that the rate of blood flow through the stomach may increase slightly at the onset of gastric-acid secretion is in accord with the findings of other workers. One of Boenheim's (1930*a*) protocols shows a similar effect, though his general conclusion was that histamine decreased blood flow. Thompson & Vane (1953) and Cutting *et al.* (1937) found that histamine increased the rate of blood flow through the cat's stomach, and suggested that the increased gastric secretion which resulted paralleled the increase in blood flow. We have been unable to confirm that the amount of gastric acid secretion is dependent upon the rate of blood flow through the stomach. There was no significant difference between the rate of flow of blood from stomachs which were actively secreting acid gastric juice and from those which did not secrete. Nor was there any significant difference between the rates of flow under basal conditions and during the continuous infusion of histamine, though since blood pressure fell as a consequence of the histamine infusion the maintenance of an unchanged rate of blood flow must have involved a decrease in peripheral resistance in the stomach vessels. It is unlikely that this decreased resistance could result from causes other than vasodilatation. Whittaker & Winton (1933) showed that the apparent viscosity of blood perfusing the dog's leg was not affected by changes in blood pressure over the range found in our experiments, but increased slightly when pressure fell below 50 mm Hg. We are aware that during gastric secretion there is a probable redistribution of circulating blood within the stomach wall, and that there may be an increased capillary flow in the mucosa and submucosa.

Intravenous infusion of adrenaline (1·0, 2·0, 4·0 or 8·0 μg/kg/min) significantly increased the rate of blood flow through the stomach, but had no significant effect on the mean rate of acid secretion of the group. However, in several individual animals (see Fig. 2) there was a marked increase in the rate of acid secretion. Also, in two cases, though the rate of blood flow increased with adrenaline this increase was accompanied by some slight degree of vasoconstriction (Fig. 1).

There is considerable difference of opinion in the literature concerning the action of adrenaline upon gastric blood flow and secretion. Of the workers who have studied both flow and secretion in the same animal Boenheim (1930*a*, *b*) showed that 'suprarenin' caused a reduction in

gastric blood flow accompanying a rise in systemic arterial pressure. Gastric motility and secretion and oxygen utilization also decreased. Thompson & Vane (1953) found that adrenaline (10 μg/min) given intravenously during the intravenous infusion of 15 μg/min of histamine reduced gastric acid secretion by 50% in the cat, although they noted that the secretory rate doubled in one animal. However, with lower doses of adrenaline (2·0 μg/min) they observed that the rate of gastric blood flow increased. They suggested that the action of adrenaline was a balance between the increased vascular resistance of the stomach and the increased perfusion pressure, declaring the action of adrenaline upon gastric secretion to be due merely to its effect on the vascular bed. Our results confirm neither of these suggestions. In all but two cases (Fig. 1) adrenaline decreased the resistance of the gastric vessels and its effects on secretory activity were not related to the effects on total gastric blood flow (Fig. 2).

Lim *et al.* (1927) reported that injections of adrenaline reduced gastric blood flow, but one of their protocols shows a doubled rate of flow during the period that blood pressure was raised, after which blood flow fell below the previous resting level only when the blood pressure had returned to normal.

Other investigations have been carried out on the action of adrenaline on the secretory response of the stomach in animals with simple gastric fistulae or pouches. Ivy & McIlvain (1923) and von Sirotinin (1924) found that giving adrenaline resulted in increased gastric secretion in the dog. Karvinen & Karvonen (1952), in dogs, and Linde (1950) in cats, obtained no effect upon the rate of histamine-induced gastric secretion from injections of adrenaline. In contrast, Hess & Gundlach (1920), using dogs equipped with Pavlov pouches, found that adrenaline decreased both the volume and acidity of the secretion. Brun (1945) claimed that adrenaline was strongly vasoconstrictor to the gastric vessels, and, since the recovery of gastric secretion from the inhibition produced by the amine was rapid, deduced that such effect as it had was due to its action on the blood vessels. This view was supported by Forrest & Code (1954), who were able to plot dose–response relations between the amount of adrenaline infused and the degree of inhibition of gastric acid secretion. Their experiments were made in dogs with Heidenhain pouches. However, the protocol provided by these authors shows that the rate of acid secretion 1 hr after an infusion of adrenaline had stopped was still only half that which obtained at the start of the experiment.

We have found that both gastric blood flow and acid secretion were significantly decreased by infusions of noradrenaline. None of the previous workers has measured these effects simultaneously, but Forrest &

Code (1954) and Harries (1956) have demonstrated the marked inhibitory effect of this amine upon histamine-induced acid secretion in the unanaesthetized dog, either in a Heidenhain pouch or from a stomach having a simple gastric fistula. Linde (1950), however, reported that noradrenaline had no effect on histamine-induced secretion from stomach pouches in cats, and Karvinen & Karvonen (1952) reported similar findings in dogs.

Our own results show that the circulatory effects of the catechol amines wore off within 2–3 min of stopping the infusions, whereas the inhibitory effects on secretion were prolonged for periods of 30 min or longer in the case of adrenaline and for up to 2–3 hr in the case of noradrenaline.

It was suggested by Harries (1958) that the lack of correlation between the time relations of the vascular and secretory effects of the catechol amines made it improbable that inhibition of secretion could be dependent on changes in gastric blood flow. He suggested that, since vagotomy decreases the secretory response of the stomach to histamine, vagal tone is largely responsible for normal gastric secretion, and that adrenaline and noradrenaline might act by inhibiting parasympathetic ganglionic activity concerned with gastric secretion. Evidence of such inhibition of parasympathetic ganglia has been given by McDougal & West (1954) and by Kosterlitz & Robinson (1957), using isolated guinea-pig ileum, and also by Tum-Suden & Marrazzi (1951), who worked with the ciliary ganglion. Harries also showed (1957) that *iso*-propylnoradrenaline, reputed to be a dilator of the mesenteric vascular bed, inhibited gastric acid secretion in the unanaesthetized dog, and that noradrenaline had a much greater inhibitory effect on vagal juice than on histamine-induced secretion.

Forrest & Code (1954) found adrenaline to be a more potent inhibitor of gastric secretion than noradrenaline, and Ahlquist (1948) stated that it was a more potent mesenteric vasoconstrictor. Our results contradict both these findings. We found that whereas noradrenaline was always vasoconstrictor, and usually an inhibitor of histamine-induced gastric secretion, adrenaline was a dilator of the stomach vessels and had a variable effect on gastric secretion. Since a differential sensitivity of the α and β effectors may exist (Green & Kepchar, 1959), it is possible that the doses given, particularly in the case of adrenaline, may be of importance in determining whether the net result gives dominance to the α constrictor or the β dilator endings. In the experiments reported here the doses of adrenaline and noradrenaline given were small (1·0–8·0 μg/kg/min): further experiments with larger doses and experiments where several different doses are given to the same animal may elucidate this point.

SUMMARY

1. A method for studying the rate of gastric blood flow in the anaesthetized dog by a method of venous effluent collection is described.

2. Simultaneous measurements of gastric blood flow and secretion are recorded.

3. The mean rate of gastric blood flow under basal conditions was 14·0 ml./100 g stomach/min (S.D. 6·0).

4. Intravenous infusions of histamine acid phosphate (2·5–10 μg/kg/min), which stimulated acid secretion by the stomach, did not significantly affect the rate of gastric blood flow, nor was there any correlation between the rate of acid secretion and rate of stomach blood flow.

5. Intravenous infusions of L-adrenaline tartrate (1·0–8·0 μg/kg/min) significantly increased gastric blood flow from a mean rate of 18·0 ml./100 g/min to a mean rate of 37·8 ml./100 g/min, while the effects of such infusions upon histamine-induced acid secretion were variable.

6. Intravenous infusions of L-noradrenaline tartrate (1·0–8·0 μg/kg/min) significantly decreased the rate of gastric blood flow from a mean rate of 20·3 ml./100 g/min to a mean rate 17·4 ml./100 g/min. Histamine-induced acid secretion was significantly decreased during such infusions.

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REFERENCES

AHLQUIST, R. P. (1948). A study of the adrenotropic receptors. *Amer. J. Physiol.* **153**, 586–600.

BEST, C. H. & TAYLOR, N. B. (1961). *The Physiological Basis of Medical Practice*, 7th ed., p. 366. London: Ballière, Tindall and Cox Ltd.

BOENHEIM, F. (1930*a*). Über das Minutenvolumen des Magens und seine Beeinflussung durch Blutdruck, durch Vagusreizung, durch Histamin und Organextracte. *Z. ges. exp. Med.* **71**, 88–107.

BOENHEIM, F. (1930*b*). Der physiologische Sauerstoffverbrauch des Magens und seine Beeinflussung durch Vagusreizung, durch Histamin und durch Organextracte. *Z. ges. exp. Med.* **71**, 108–117.

BRUN, G. C. (1945). Variations in the diameter of abdominal arteries after intravenous injection of adrenaline. *Acta pharm. tox., Kbh.*, **1**, 403–419.

BURTON-OPITZ, R. (1910). Über die Stromung des Blutes in dem Gebiete der Pfortader. III. Das Stromvolumen der Vena gastrica. *Pflüg. Arch. ges. Physiol.* **135**, 205–244.

CUMMING, J. D., HAIGH, A. L., HARRIES, E. H. L. & NUTT, M. E. (1961). The measurement of total gastric blood flow and its relationship to gastric acid secretion in the anaesthetized dog. *J. Physiol.* **157**, 39*P*.

CUTTING, W. C., DODDS, E. C., NOBLE, R. L. & WILLIAMS, P. C. (1937). The effect of alteration in blood flow on gastric secretion. *Proc. Roy. Soc.* B, **123**, 39–48.

FORREST, A. P. M. & CODE, C. F. (1954). The inhibiting effect of epinephrine and norepinephrine on secretion induced by histamine in separated pouches of dogs. *Pharm. J.* **110**, 447–450.

GEBER, W. F. (1960). Quantitative measurement of blood flow in various areas of small and large intestine. *Amer. J. Physiol.* **198**, 985–986.

GREEN, H. D. & KEPCHAR, J. H. (1959). Control of peripheral resistance in major systemic vascular beds. *Physiol. Rev.* **39**, 617–686.

HAIGH, A. L. & SANDLAND, P. (1961). A simple blood flowmeter. *J. Physiol.* **159**, 53–54*P*.

HARRIES, E. H. L. (1956). The effect of noradrenaline on the gastric secretory response to histamine in the dog. *J. Physiol.* **133**, 498–505.

HARRIES, E. H. L. (1957). The mode of action of sympathomimetic amines in inhibiting gastric secretion. *J. Physiol.* **138**, 48–50*P*.

HARRIES, E. H. L. (1958). *Studies on gastric secretion.* Ph.D. thesis. University of London.

HERRICK, J. F., ESSEX, H. E., MANN, F. C. & BALDES, E. J. (1934). The effect of digestion on the blood flow in certain blood vessels of the dog. *Amer. J. Physiol.* **108**, 621–628.

HESS, W. R. & GUNDLACH, R. (1920). Der Einfluss des Adrenalins auf die Sekretion des Magensaftes. *Plüg. Arch. ges. Physiol.* **185**, 122–136.

IVY, A. C. & MCILVAIN, G. B. (1923). The excitation of gastric secretion by application of substances to the duodenal and jejunal mucosa. *Amer. J. Physiol.* **67**, 124–140.

KARVINEN, E. & KARVONEN, M. J. (1952). Effect of insulin hypoglycaemia on histamine-induced Heidenhain pouch secretion in dogs. *Acta physiol. scand.* **27**, 350–370.

KOSTERLITZ, H. W. & ROBINSON, J. A. (1957). Inhibition of the peristaltic reflex of the isolated guinea-pig ileum. *J. Physiol.* **136**, 249–262.

LIM, R. K. S., NECHELES, H. & NI, T. G. (1927). The vasomotor reactions of the viviperfused stomach. *Chin. J. Physiol.* **1**, 381–396.

LINDE, S. (1950). Studies on the stimulation mechanism of gastric secretion. *Acta physiol. scand.* **21**, Suppl. 74, 1–88.

MCDOUGAL, M. D. & WEST, G. B. (1954). The inhibition of the peristaltic reflex by sympathomimetic amines. *Brit. J. Pharmacol.* **9**, 131–137.

NI, T. G. & LIM, R. K. S. (1928). The gas and sugar metabolism of the viviperfused stomach. *Chin. J. Physiol.* **2**, 45–86.

VON SIROTININ, G. W. (1924). Über die Wirkung des Adrenalins auf die Sekretion des Magensaftes aus dem nach Heidenhain isolierten kleinen Magen des Hundes. *Z. ges. exp. Med.* **40**, 90–97.

THOMPSON, J. E. & VANE, J. R. (1953). Gastric secretion induced by histamine and its relationship to blood flow. *J. Physiol.* **121**, 433–444.

TUM-SUDEN, C. & MARRAZZI, A. S. (1951). Synaptic inhibitory action of adrenaline at parasympathetic synapses. *Fed. Proc.* **10**, 138.

WHITTAKER, S. R. F. & WINTON, F. R. (1933). The apparent viscosity of blood flowing in the isolated hind limb of the dog and its variation with corpuscular concentration. *J. Physiol.* **78**, 339–369.

WILLOX, G. L., MICHALYSHYN, B. & KOWALEWSKI, K. (1961). Gastric blood flow and temperature after histamine in dogs. *Arch. int. Physiol.* **69**, 668–676.