Br. J. Pharmac. (1972), **46**, 225–233.

The effects of isoprenaline and noradrenaline on pentagastrin-stimulated gastric acid secretion and mucosal blood flow in the dog

B. P. CURWAIN AND PAMELA HOLTON

Department of Physiology, St. Mary's Hospital Medical School, London W.2

Summary

1. Isoprenaline (0·02 to 2·0 μg kg^{-1} min^{-1}) inhibited gastric secretion in response to pentagastrin in both conscious and anaesthetized dogs and in response to feeding in conscious dogs.

2. The inhibition was unaffected during cardiac β-adrenoceptor blockade by propranolol.

3. The inhibition was not due to decreased mucosal blood flow.

4. This effect of isoprenaline is different from its effect on histamine-induced gastric secretion.

5. Noradrenaline (0·05–2·0 μg kg^{-1} min^{-1}) also decreased gastric secretion but it was less effective than isoprenaline.

6. The mechanism of action of noradrenaline is probably a decrease in mucosal blood flow.

Introduction

The effect of an adrenoceptor stimulant drug on gastric secretion depends on many factors, particularly whether it acts on α- or β-receptors and whether secretion is induced by histamine or by gastrin-like compounds. This field has recently been reviewed by Holton (1972). The mechanism of action of noradrenaline, an α-adrenoceptor agonist, appears to be primarily by the production of a decrease in mucosal blood flow (Jacobson, 1970). The mechanism of action of the β-adrenoceptor agonist, isoprenaline, is more complex. On a background of histamine stimulation, small doses of isoprenaline increase or do not affect secretion (Jacobson, Linford & Grossman, 1966; Curwain, Endersby & Holton, 1971), while causing increased mucosal blood flow (Jacobson *et al.*, 1966). Larger doses of isoprenaline in conscious dogs decrease histamine-induced secretion (Harries, 1957; Pradhan & Wingate, 1962; Jacobson *et al.*, 1966; Curwain *et al.*, 1971) and mucosal blood flow (Jacobson *et al.*, 1966) but increase histamine-induced secretion in anaesthetized dogs (Curwain *et al.*, 1971). The effect of isoprenaline on secretion induced by secretagogues other than histamine, has been less often investigated. Harries (1957) showed that histamine-induced secretion is less sensitive to inhibition by noradrenaline than is insulin-induced secretion but he did not study relative sensitivity to isoprenaline. Pradhan & Wingate (1962) extended Harries's observations and confirmed his findings that histamine-induced secretion is relatively insensitive to inhibition and showed further that isoprenaline, which

was a more potent inhibitor of secretion than noradrenaline or adrenaline, was also more effective against secretion induced by non-histamine stimulants than against histamine-induced secretion.

We have confirmed that isoprenaline has a greater inhibitory effect on acid secretion induced by pentagastrin and by feeding and we have analysed this effect in terms of gastric mucosal blood flow. Evidence is presented suggesting that in these conditions the observed inhibition of secretion is not secondary to decreased mucosal blood flow. We have also compared the effects of isoprenaline and noradrenaline and have obtained evidence that the mechanisms of action of these drugs are different.

Methods

Experiments on conscious dogs

Heidenhain pouches were prepared in healthy female dogs (10–15 kg) several weeks before the experiments. Food was withheld but water allowed 18 h before each experiment. On the day of the experiment intravenous catheters were inserted with aseptic precautions. One catheter (0·63 mm outside diameter) was used for infusion of saline at 1 ml min^{-1} throughout the experiment; drugs were added to the saline. Mucosal blood flow was estimated by radioactive aniline clearance (Curwain & Holton, 1971; Curwain, 1972a). The aniline was added to the saline infusion. Blood samples were withdrawn at 30 min intervals via a second vein catheter (0·92 mm outside diameter). Gastric juice was collected at 10 or 15 min intervals and aliquots were titrated against 0·1 N NaOH with phenolphthalein as indicator.

Measurement of gastric acid secretion in anaesthetized dogs

Two dogs each weighing 9 kg were used. Anaesthesia was induced by intravenous pentobarbitone sodium (30 mg/kg) and a polythene catheter was introduced into a superficial vein in one fore-leg for the administration of further anaesthetic as required. The stomach was exposed through a mid-line laparotomy and the pylorus divided between stout ligatures excluding the right gastric artery. A stainless steel cannula (diameter 2 cm) was introduced into the most dependent portion of the greater curvature and secured with two purse string sutures. The cannula was brought out through a stab wound in the abdominal wall and the incision closed. Handling of the stomach was kept to a minimum during the operation.

A femoral vein was then cannulated for the infusion of pentagastrin and isoprenaline and a femoral artery was connected, via catheter, to a Devices blood pressure transducer. Blood pressure was recorded on an S.E. 2100 Ultraviolet recorder.

A third experiment was carried out with one of the pouch dogs in a terminal experiment. In this experiment gastric secretion was collected from the main stomach via a cannula secured into the pylorus as well as from the pouch.

The following drugs were used: (±)-isoprenaline sulphate, (−)-noradrenaline acid tartrate (Levophed, Bayer), (±)-propranolol hydrochloride (Inderal, ICI), (−)-phenylephrine hydrochloride (Koch-Light Laboratories), phentolamine mesylate (Rogitine, Ciba).

Results

Pentagastrin-induced secretion in conscious dogs

In 10 experiments in 4 dogs a plateau of acid secretion was established by a pentagastrin infusion (4 or 5 μg kg^{-1} h^{-1}). On each occasion the addition of a small dose of isoprenaline caused a marked decrease in secretion; 0·05 μg kg^{-1} min^{-1} decreased secretion to a mean of 44% and 0·2 μg kg^{-1} min^{-1} to a mean of 10% of the control plateau. This result is in contrast to the effect of isoprenaline

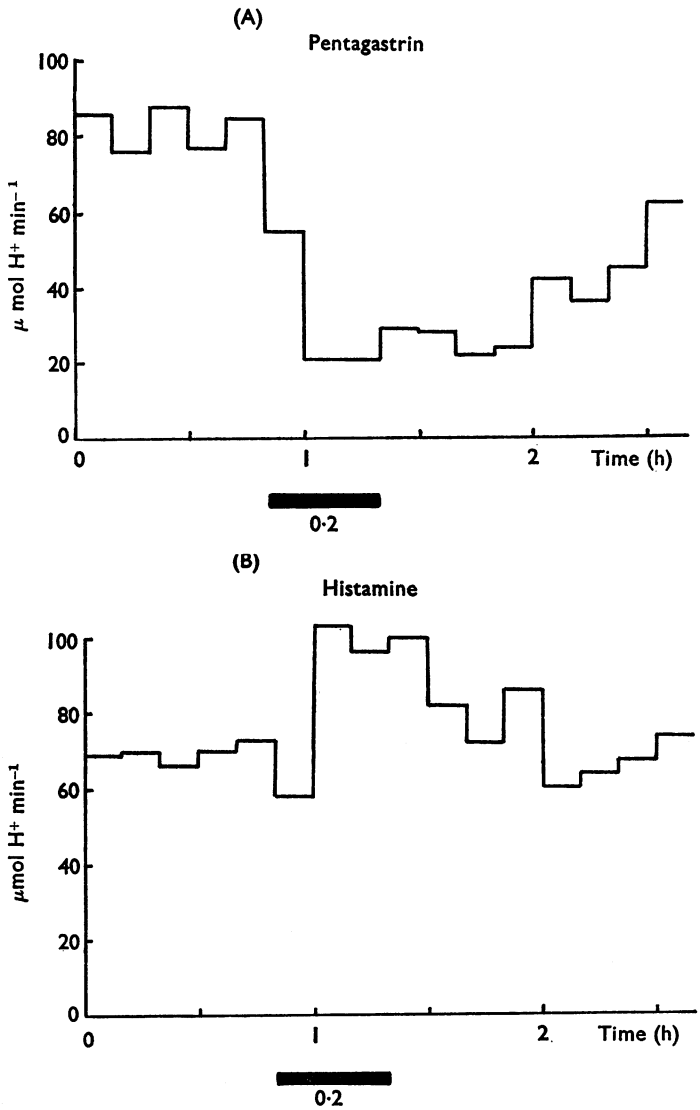

FIG. 1. Conscious dog with Heidenhain pouch. Secretory responses of the same dog in two experiments. Isoprenaline (0·2 μg kg^{-1} min^{-1}) was infused intravenously during the period indicated by the black bars in both experiments. In A secretion was induced by pentagastrin (5 μg kg^{-1} h^{-1}) and was decreased by isoprenaline. In B secretion was induced by histamine acid phosphate (2 μg kg^{-1} min^{-1}) and was increased by isoprenaline. Ordinates: Acid secretion μmol H$^+$ min^{-1}. Abscissae: Time, h.

on histamine-induced secretion where these small doses of isoprenaline either have no effect or cause a slight increase in secretion (Curwain *et al.*, 1971). The contrast is illustrated in Fig. 1 which shows the responses of the same dog to the same dose of isoprenaline given during secretion in response to pentagastrin and to histamine.

Secretion induced by feeding

In these experiments a secretory plateau was established by feeding with a standard meal. In each of 6 experiments in 4 dogs the infusion of isoprenaline (0·1–0·25 μg kg^{-1} min^{-1}) for 10–30 min decreased acid secretion to a mean of 17% of the plateau.

Inhibition of secretion by noradrenaline and phenylephrine

Noradrenaline had a similar effect on secretion induced by pentagastrin or feeding. In each of 5 experiments in 3 dogs noradrenaline (0·2 μg kg^{-1} min^{-1}) decreased pentagastrin-induced secretion to a mean of 29% of the control period. Similarly noradrenaline decreased the plateau of secretion after feeding. In one experiment 0·1 μg kg^{-1} min^{-1} for 10 min decreased it to 67% and in another dog 0·5 μg kg^{-1} min^{-1} for 10 min decreased it to 15% of control levels. Secretion was induced by histamine in three experiments and noradrenaline was infused for 30 min; 0·2 μg kg^{-1} min^{-1} had no effect but 1·0 μg kg^{-1} min^{-1} and 2·0 μg kg^{-1} min^{-1} decreased secretion to a mean of 85% and 20% respectively. After administration of phentolamine (5 mg kg^{-1} and 5 mg kg^{-1} h^{-1}) gastric secretion was profoundly depressed and was not further decreased by noradrenaline. In three experiments secretion was induced with pentagastrin and phenylephrine was given in doses of 10 and 20 μg kg^{-1} min^{-1} which are equipressor with 1 and 2 μg kg^{-1} min^{-1} of noradrenaline (Bowman, Rand & West, 1968). The secretion was inhibited to a mean of 50% and 25% respectively.

The effect of β-adrenoceptor blockade

Propranolol (1–2 mg kg^{-1} i.v.) was given 30–80 min before the isoprenaline infusion in order to block β-adrenoceptors. In each of 5 experiments the inhibition of pentagastrin-induced secretion produced by a subsequent infusion of isoprenaline was as great as in the absence of β-adrenoceptor blockade. This result is illus-

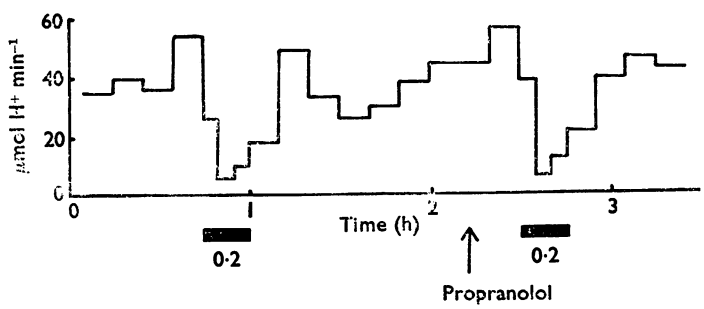

FIG. 2. Conscious dog with Heidenhain pouch. Inhibition of pentagastrin-induced gastric secretion by isoprenaline (0·2 μg kg^{-1} min^{-1}) given during the black bars before and after β-adrenoceptor blockade by propranolol (1 mg/kg i.v.) given at the arrow. The dog's heart rate increased during the first but not during the second isoprenaline infusion. Ordinates: Acid secretion μmol H$^+$ min^{-1}. Abscissae: Time, h.

trated in Figure 2. Evidence that propranolol was effective in blocking cardiac receptors in these experiments was obtained from measurements of heart rate which was unaffected by isoprenaline during this period. It is also noteworthy that this dose of propranolol completely abolished the decrease in gastric secretion produced by 10 times larger doses (2 μg kg^{-1} min^{-1}) of isoprenaline during histamine stimulation (Curwain *et al.*, 1971).

Pentagastrin-induced secretion in acutely prepared anaesthetized dogs

The effect of isoprenaline (0·2 μg kg^{-1} min^{-1}) was studied in 3 experiments on acutely prepared anaesthetized dogs in which a secretory plateau was established with pentagastrin. On each occasion secretion decreased markedly, the mean secretion during isoprenaline being 7% of the plateau. This is illustrated in Fig. 3 and is again in contrast to the stimulating effect of isoprenaline on histamine-induced secretion in acutely prepared anaesthetized dogs (Curwain *et al.*, 1971).

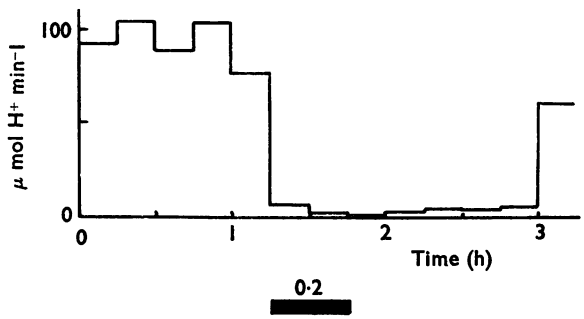

FIG. 3. Anaesthetized dog 9 kg (pentobarbitone sodium) innervated whole stomach. Inhibition of pentagastrin-induced gastric secretion by isoprenaline (0·2 μg kg^{-1} min^{-1} during the black bar). Ordinates: Acid secretion μmol H$^+$ min^{-1}. Abscissae: Time, h.

The effects of isoprenaline and noradrenaline on gastric mucosal blood flow during pentagastrin-induced secretion in conscious dogs

In these experiments a plateau of secretion in response to pentagastrin was established and then isoprenaline (0·05–0·2 μg kg^{-1} min^{-1}) in 5 experiments or noradrenaline (0·1–0·5 μg kg^{-1} min^{-1}) in 5 experiments was infused. Gastric mucosal blood flow fell during the decrease in acid secretion in response to either of these drugs as is illustrated in Figure 4A. However, the nature of the responses to the two catecholamines was different. When isoprenaline was infused the ratio (G/P) of mucosal blood flow to secretion increased whereas during noradrenaline administration mucosal blood flow and secretion were affected equally and the ratio remained unchanged (Fig. 4B).

Discussion

The results are summarized in Table 1, which also includes results from other publications from this laboratory. They show that in the dog gastric secretion in response to pentagastrin or endogenous gastrin (after feeding) is very sensitive to inhibition by small doses of isoprenaline. This is true both in the conscious dog and in the acutely-prepared anaesthetized dog. The fact that the results are obtained equally well under anaesthesia and in vagally-denervated pouches suggests

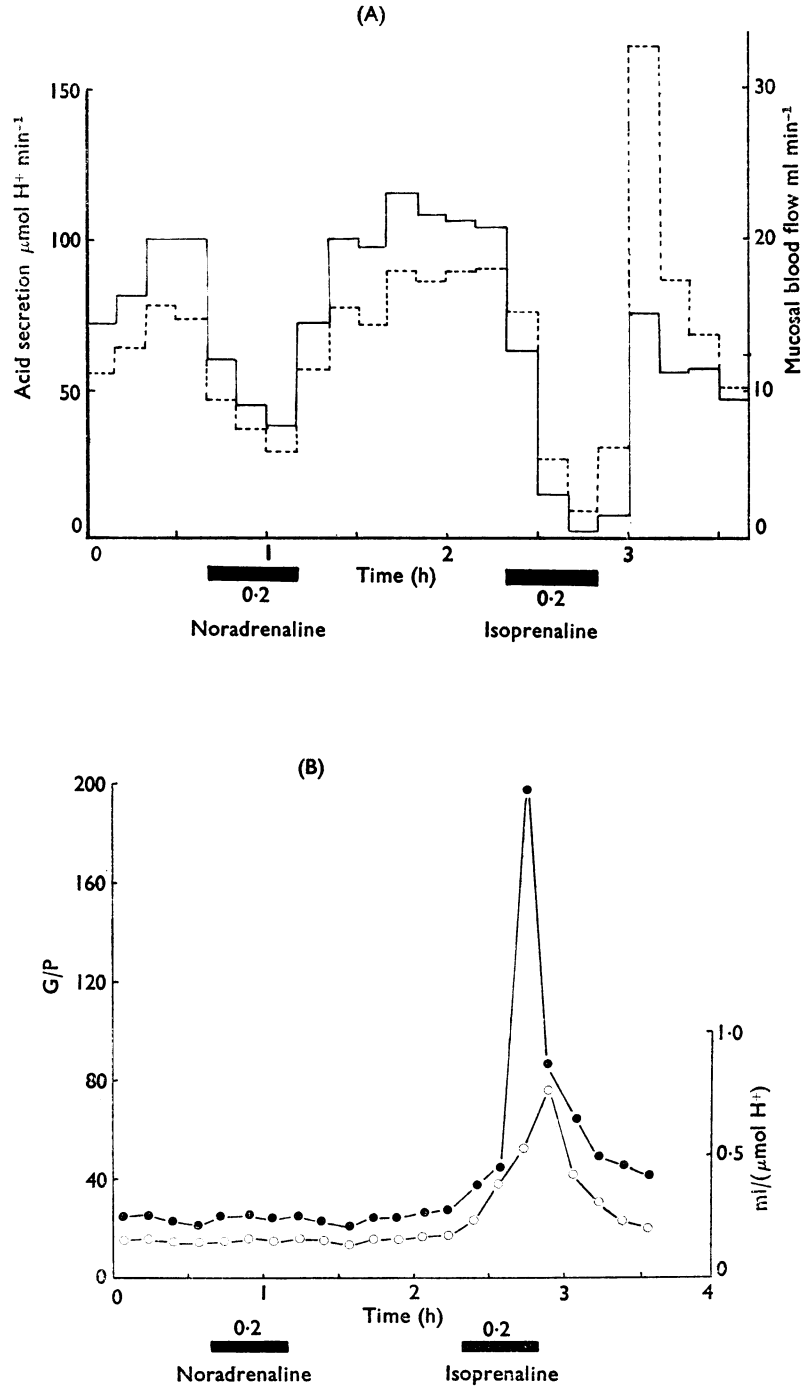

FIG. 4. Conscious dog with Heidenhain pouch. (A) The effect of noradrenaline (0·2 μg kg^{-1} min $^{-1}$) and isoprenaline (0·2 μg kg^{-1} min^{-1}) on gastric acid secretion in μmol H$^+$ min^{-1} (left hand scale and solid line) and mucosal blood flow in ml min^{-1} aniline clearance (right hand scale and interrupted line). (B) The ratio of mucosal blood flow to secretory volume G/P (left hand scale and filled circles) and mucosal blood flow to acid secretion (right hand scale and open circles) calculated for the experiment shown in (A). The ratios were constant during noradrenaline infusion but increased during and after isoprenaline.

TABLE 1. *The effects in conscious dogs of small and large doses of isoprenaline and noradrenaline on gastric secretion and G/P* during secretion in response to different stimuli*

	Isoprenaline					Noradrenaline			
	Small dose 0·05–0·25 μg kg^{-1} min^{-1}			Large dose 0·5–2 μg kg^{-1} min^{-1}		Small dose 0·1–0·5 μg kg^{-1} min^{-1}		Large dose 1–2 μg kg^{-1} min^{-1}	
	Secretion	Secretion after propranolol	G/P	Secretion	Secretion after propranolol	Secretion	G/P	Secretion	G/P
Histamine	↑ or 0[1]			↓[1]	0[1]	0		↓[2]	↓[2]
Pentagastrin	↓	↓	↑			↓	0		
Feeding	↓		↑			↓			

* G/P: ratio of mucosal blood flow to secretory volume. [1] Curwain *et al.*, 1971. [2] Curwain, 1972c.

that the effect of isoprenaline is not reflex. The persistence of the response in the presence of propranolol, which abolished the effect of isoprenaline on the heart rate and presumably also on arterial blood pressure, suggests that the effect of isoprenaline is not due to decreased mucosal blood flow. This is confirmed by the finding that the ratio of mucosal blood flow to secretion actually increases in response to isoprenaline.

It was pointed out by Jacobson (1970) that any procedure which causes a decrease in acid secretion is likely to cause a decrease in mucosal blood flow because the level of blood flow is controlled by the metabolic requirements of the secretory tissue. In a comparison of the effects of noradrenaline and a prostaglandin, Jacobson concluded that the prostaglandin probably had a direct action on secretion because it increased the ratio of blood flow to secretion. The ratio of blood flow to secretion is increased even more markedly in our experiments with isoprenaline thus establishing that the action of isoprenaline on pentagastrin-induced secretion is not due to decreased mucosal blood flow. This conclusion is in agreement with the suggestion of Harries (1957) that isoprenaline had a direct inhibitory action on the secretory mechanism.

Since we do not know the position of the gastrin (and pentagastrin) receptors or whether they are on the oxyntic cells themselves or some more distant cells, we cannot speculate about the locus of action of isoprenaline. However, the difference in sensitivity of histamine-induced secretion and gastrin-induced secretion to inhibition by isoprenaline supports the hypothesis that isoprenaline acts on the gastrin receptors. It is worth noting that the combination of propranolol and isoprenaline produces an antigastrin effect together with relative mucosal vasodilatation. This property might have clinical application.

Isoprenaline prevents histamine liberation by antigen from sensitized tissue (Assem & Schild, 1969). Therefore the antigastrin activity of isoprenaline might be interpreted as evidence suggesting that the mechanism of action of gastrin also involved liberation of histamine. However, the antianaphylactic action of isoprenaline is readily blocked by β-adrenoceptor blocking agents (Assem & Schild, 1971) whereas the antigastrin activity is not. It is therefore unlikely that the action of gastrin is analogous to the action of antigen in the anaphylactic reaction.

The effect of isoprenaline on histamine-induced secretion is different. About 10 times as much isoprenaline is needed to decrease secretion, the decrease is blocked by propranolol and the response in anaesthetized dogs is an enhancement rather than a decrease in secretion (Curwain *et al.*, 1971). We have therefore confirmed the findings of Harries (1957) and of Pradhan & Wingate (1962) that hist-

amine-induced secretion is less easily inhibited than secretion induced by other means. The mechanism of action of isoprenaline on histamine-induced secretion needs further investigation. The possibility of a primary vascular action of isoprenaline in these circumstances has not yet been excluded.

Our results with noradrenaline confirm those of previous workers. Gastric secretion is more readily decreased by small doses of noradrenaline when it is induced by pentagastrin or gastrin than when it is induced by histamine. In this respect noradrenaline resembles isoprenaline but there is evidence that its mechanism of action is different. The action of noradrenaline is probably not due to its weak activity on β-adrenoceptors because phenylephrine, which has very little action on β-adrenoceptors (Goth, 1966) was as effective as noradrenaline in decreasing gastric secretion. It is likely that the effect of noradrenaline on gastric secretion induced by any means is secondary to vasoconstriction which would decrease mucosal blood flow below the level required by the actively metabolizing secretory tissue. The greater depression of pentagastrin-induced gastric secretion by noradrenaline may be associated with the relatively small mucosal blood flow in these conditions. Histamine, on the other hand, causes vasodilatation in excess of that needed to support gastric secretion (Jacobson & Chang, 1969; Reed & Smy, 1971; Curwain, 1972b) so that a vasoconstrictor drug is less likely to affect histamine-induced secretion. Our results are therefore compatible with Jacobson's suggestion that noradrenaline acts primarily by decreasing mucosal blood flow. In our experiments there was no increase in the ratio of blood flow to secretion when noradrenaline was given on a background of pentagastrin. In Jacobson's experiments on pentagastrin-induced secretion from gastric fistulae a significant decrease in the ratio was observed with a relatively large dose of noradrenaline. When histamine was used to stimulate secretion noradrenaline decreased the ratio of mucosal blood flow to secretion to a greater extent than in pentagastrin-induced secretion. We have confirmed this finding (Curwain, 1972c). This is compatible with the hypothesis that noradrenaline acts primarily by decreasing mucosal blood flow.

We are grateful to Mr. A. R. Scott who did the experiment illustrated in Figure 3. This research was supported by a grant from the Medical Research Council.

REFERENCES

ASSEM, E. S. K. & SCHILD, H. O. (1969). Inhibition by sympathomimetic amines of histamine release induced by antigen in passively sensitized human lung. *Nature, Lond.*, **224**, 1028–1029.

ASSEM, E. S. K. & SCHILD, H. O. (1971). Antagonism by β-adrenoceptor blocking agents of the antianaphylactic effect of isoprenaline. *Br. J. Pharmac.*, **42**, 620–630.

BOWMAN, W. C., RAND, M. J. & WEST, G. B. (1968). *Text Book of Pharmacology*, p. 747. London: Blackwell.

CURWAIN, B. P. (1972a). Comparison of the plasma clearances of aniline and amidopyrine for the measurement of gastric mucosal blood flow. *J. Physiol. (Lond.)*, **222**, 1–3*P*.

CURWAIN, B. P. (1972b). A comparison of gastric mucosal blood flow relative to gastric acid secretion in response to different stimuli in conscious dogs. *J. Physiol. (Lond.)*, 1972. In press.

CURWAIN, B. P. (1972c). The effect of feeding and drugs on gastric mucosal blood flow estimated by the clearance of radioactive aniline and its relationship to gastric acid secretion in dogs. Ph.D. Thesis University of London.

CURWAIN, B. P., ENDERSBY, K. & HOLTON, P. (1971). Effect of isoprenaline on histamine induced gastric acid secretion in dogs. *Br. J. Pharmac.*, **41**, 384*P*.

CURWAIN, B. P. & HOLTON, P. (1971). Radioactive aniline clearance from canine gastric pouches for the measurement of gastric mucosal blood flow. *Br. J. Pharmac.*, **41**, 384*P*.

GOTH, A. (1966). *Medical Pharmacology*, p. 74. St. Louis, U.S.A.: C. V. Mosby Co.

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

HOLTON, P. (1972). Catecholamines and gastric secretion. In: *The Pharmacology of Gastro-Intestinal Motility and Secretion*. ed. P. Holton. Section 39a. International Encyclopedia of Pharmacology and Therapeutics. Oxford: Pergamon.

JACOBSON, E. D., LINFORD, R. H. & GROSSMAN, M. I. (1966). Gastric secretion in relation to mucosal blood flow studied by a clearance technic. *J. clin. Invest.*, **45**, 1–13.

JACOBSON, E. D. & CHANG, A. C. K. (1969). Comparison of gastrin and histamine on gastric mucosal blood flow. *Proc. Soc. exp. Biol. Med.*, **130**, 484–486.

JACOBSON, E. D. (1970). Comparison of prostaglandin El and norepinephrine on the gastric mucosal circulation. *Proc. Soc. exp. Biol. Med.*, **133**, 516–519.

PRADHAN, S. N. & WINGATE, H. W. (1962). Effects of adrenergic agents on gastric secretion in dogs. *Archs int. Pharmacodyn. Thér*, **140**, 388–407.

REED, J. D. & SMY, J. R. (1971). Mechanisms relating gastric acid secretion and mucosal blood flow during gastrin and histamine stimulation. *J. Physiol. (Lond.)*, **219**, 571–585.

(*Received June* 1, 1972)