Br. J. Pharmac. (1977), **60**, 455–460

MECHANISMS UNDERLYING GASTRIC MUCOSAL DAMAGE INDUCED BY INDOMETHACIN AND BILE-SALTS, AND THE ACTIONS OF PROSTAGLANDINS

B.J.R. WHITTLE[1]

Department of Pharmacology, Institute of Basic Medical Sciences, Royal College of Surgeons of England, London WC2A 3PN

1 The mechanisms by which the bile salt, sodium taurocholate, potentiates the formation of gastric mucosal erosions induced by indomethacin has been investigated in the rat.

2 Systemic administration of indomethacin lowered resting mucosal blood flow but had no effect on the acid back-diffusion across the mucosa.

3 Gastric perfusion of taurocholate in acid solution increased acid back-diffusion and lowered the potential difference. This was accompanied by an increase in mucosal blood flow, which may represent a protective mechanism in the mucosa.

4 Administration of indomethacin during acid-taurocholate perfusion reduced this elevated mucosal blood flow without any further change in acid back-diffusion.

5 The results suggest that although a decrease in mucosal blood flow or an increase in acid back-diffusion can lead to a low incidence of erosions, a combination of both produces extensive mucosal damage.

6 The (15S)-methyl analogue of prostaglandin E_2 reduced erosion formation induced by indomethacin and acid-taurocholate administration.

7 It is suggested that this protective action of the prostaglandin analogue may be linked to changes in gastric mucosal permeability and in mucosal blood flow.

Introduction

The presence of endogenous bile in the gastric lumen has been implicated in the pathogenesis of the acute gastric lesions which follow administration of non-steroid anti-inflammatory agents (Abtahi & Djahanguiri, 1975). Furthermore, the administration of bile acids or salts into the gastric lumen greatly increases the formation of gastric mucosal erosions following intragastric or systemic administration of aspirin-like drugs in rats (Semple & Russell, 1975; Whittle, 1975). In the present study, changes in gastric mucosal blood flow and in the resistance of the mucosa to acid back-diffusion have been investigated as possible mechanisms underlying such acute erosion formation in the rat. In addition, since prostaglandin E_2 methyl analogues can prevent this mucosal damage (Carmichael, Nelson, Russell, Chandra, Lyon & Cochran, 1976; Whittle, 1976a), the effects of the prostaglandin analogue on these parameters have also been studied.

[1] Present address: Department of Pharmacology, Wellcome Research Laboratories, Langley Court, Beckenham, Kent BR3 3BS.

A preliminary account of this work has been presented to the British Pharmacological Society (Whittle, 1976b).

Methods

Determination of acid back-diffusion

The gastric lumen of the rat (anaesthetized with urethane) was perfused (0.1–0.2 ml/min) with acid-saline using the techniques described in detail by Main & Whittle (1973a). Acid back-diffusion across the mucosa was determined by titration of the gastric perfusate and the perfusing fluid with an autoburette (Radiometer, Copenhagen). The decrease in the titratable acid concentration following perfusion was expressed as acid-loss, μEq/minute.

Measurement of potential difference

Potential difference across the mucosa was determined with balanced calomel electrodes (Beckman-R11C,

Ltd.) connected by polyethylene catheters (Miniven, Portex Ltd.) filled with saturated potassium chloride solution, and agar (4% w/v) to the outflow cannula from the gastric lumen and to either the cannula in a femoral vein, or to a subcutaneous saline-filled bleb. Potential difference was continuously recorded with a millivoltmeter (Comark Electronics Ltd.) and displayed on a chart-recorder (Devices; MX2).

Gastric mucosal blood flow

Changes in mucosal blood flow were determined by the [^{14}C]-aniline clearance technique (Main & Whittle, 1973a) and expressed as percentage of the values obtained during the control periods.

Assessment of gastric mucosal erosions

The perfused stomachs were removed at the end of the experimental period, opened along the lesser curvature and pinned flat on a cork board. Erosions, which formed in the glandular mucosa, were counted and each one given a severity rating on a 1–3 scale as previously described (Main & Whittle, 1975a). The total, divided by 10, was the 'erosion index' for that stomach.

Drugs

Indomethacin (Merck, Sharp & Dohme, Ltd.) was dissolved in 5% w/v sodium bicarbonate solution (pH 8) to give a final concentration of 10–20 mg/ml, and immediately injected subcutaneously. For intravenous injection, this indomethacin solution was diluted (1 volume in 4 volumes) with distilled water (an isotonic solution of sodium bicarbonate being 1.26% w/v).

Crude sodium taurocholate (Sigma Chemical Co.) dissolved in distilled water, was added to acid saline, filtered (Whatman No. 1 paper), centrifuged (1000 *g* for 5 min) and the supernatant diluted to give the desired acid and bile-salt concentration. In experiments with acid and acid-taurocholate perfusion, the acid-taurocholate solution was adjusted to give the same titre as the control acid solution. The final bile-salt concentration was expressed in terms of the sodium taurocholate content of the crude material.
Prostaglandins, stored in methanol (−5°C) were made up freshly in 0.9% w/v NaCl solution (saline) following evaporation of the methanol when required and injected subcutaneously or by intravenous infusion.

Statistical analysis

Results are expressed as the mean ± s.e. mean where (n) is the number of values in the group. The significance of the data was evaluated using Student's t test for paired and non-paired data and also the non-parametric Mann-Whitney U-test, where appropriate. $P<0.05$ was taken as significant.

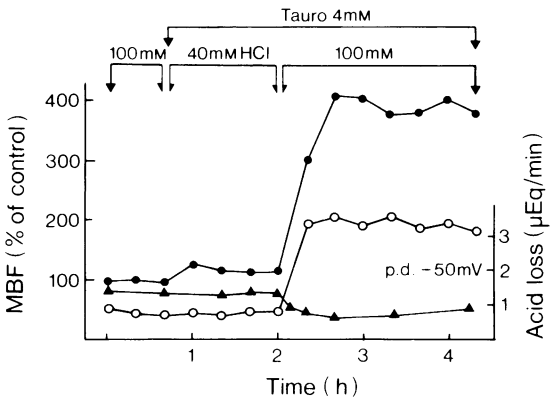

Figure 1 Effects of acid saline (HCl, 40–100 mM) and taurocholate (Tauro, 4 mM) perfusion on gastric mucosal blood flow (MBF, ●, left ordinate scale), acid-loss (○, right ordinate scale) and potential difference (p.d., ▲, right ordinate scale).

Results

Formation of gastric mucosal erosions

Perfusion of the gastric lumen for 3 h with acid-saline (100 mM HCl, pH 1) did not result in damage to the mucosa. Indomethacin (20 mg/kg, s.c.), administered at the start of the acid perfusion led to a small, variable incidence of erosions after 3 h, (the erosion index was 1.1 ± 0.8, $n=3$). Gastric perfusion of the bile salt, sodium taurocholate (2 mM) in acid solution (100 mM HCl) also gave a low 3 h-erosion index (0.5 ± 0.1, $n=3$). However, as shown previously (Whittle, 1976a), administration of indomethacin at the start of the acid-taurocholate perfusion led to a significant potentiation of erosion formation (the erosion index was 6.5 ± 0.4, $n=5$; $P<0.001$).

Effect of bile salt on acid back-diffusion

During gastric perfusion (0.1–0.2 ml/min) with acid saline during control periods, there was always a detectable and consistent acid back-diffusion across the mucosa (Figure 1). This resting acid back-diffusion was dependent on the acid concentration (10–100 mM HCl; 8 observations) of the perfusing fluid. The overall resting acid loss during 3 h perfusion with acid saline (100 mM HCl) was 152 ± 29 μEq/min ($n=3$).

The resting back-diffusion of acid was significantly ($P<0.001$) increased by perfusion with taurocholate

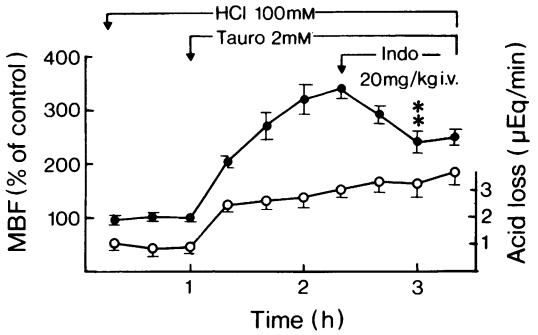

Figure 2 Effects of indomethacin (Indo) administration (20 mg/kg, i.v.) on mucosal blood flow (MBF, ●, left ordinate scale) and acid-loss (○, right ordinate scale) during taurocholate (Tauro, 2 mM) and acid (HCl, 100 mM) perfusion. Results are mean of four experiments. Vertical lines show s.e. mean. $^{**}P<0.01$.

(2 mM) in acid solution (100 mM HCl), and was independent of the rate of perfusion; an increase in acid loss from 0.9 ± 0.4 to 2.5 ± 0.2 μEq/min after 1 h ($n=3$) was observed when the perfusion rate was 0.1 ml/min, and an increase from 0.9 ± 0.2 to 2.6 ± 0.3 μEq/min ($n=5$) was seen at a perfusion rate of 0.2 ml/minute. For subsequent studies, a perfusion rate of 0.2 ml/min was employed.

In a further three experiments, the acid loss appeared to be dependent both on the acid concentration (60–120 mM HCl) and the taurocholate concentration (1–10 mM). In the experiment illustrated in Figure 1, perfusion of taurocholate (4 mM) with a low acid concentration (40 mM HCl) had little effect on acid loss, whereas a marked increase was seen when the acid concentration was raised to 100 mM HCl.

Effect of indomethacin on acid back-diffusion

During perfusion of acid saline (100 mM HCl), intravenous administration of indomethacin (20 mg/kg over 10 min) had no consistent effect on acid back-diffusion across the mucosa; in 4 experiments the resting acid-loss (0.93 ± 0.12 μEq/min) was similar to that 1 h after indomethacin (0.98 ± 0.13 μEq/min, $P<0.05$).

When indomethacin (20 mg/kg, s.c.) was administered at the start of gastric perfusion of taurocholate (2 mM) in acid solution, the overall loss of acid across the mucosa was 458 ± 39 μEq/3 h ($n=5$) compared with 364 ± 55 μEq/3 h ($n=5$; $P<0.05$) for taurocholate perfusion alone. In 4 other experiments where indomethacin was injected intravenously during acid-taurocholate perfusion, there was no significant increase in the acid-loss determined at 20 min intervals for 1 h (Figure 2).

Changes in potential difference (p.d.)

In eight experiments during acid-saline perfusion (pH 1), the resting p.d. (-42.3 ± 1.2 mV) rapidly fell, following perfusion of taurocholate (2 mM at pH 1) to -32.6 ± 1.5 mV after 10 min ($P<0.001$). As shown in Figure 1, the p.d. tended to return towards resting values during the continued perfusion of taurocholate.

During acid-saline perfusion, indomethacin (20 mg/kg, i.v.) had no consistent effect on p.d. (3 observations).

Effects of indomethacin on mucosal blood flow

As previously observed (Main & Whittle, 1975a), indomethacin decreased resting gastric mucosal blood flow; in the present experiments during acid-saline perfusion (100 mM HCl), intravenous injection of indomethacin (20 mg/kg over 10 min) caused a significant ($P<0.01$) fall in mucosal blood flow by $20 \pm 5\%$ of the control value, after 1 h ($n=5$).

Effects of taurocholate on mucosal blood flow

Perfusion of taurocholate (1–10 mM) in acid saline (60–120 mM HCl) caused a marked increase in mucosal blood flow (Figure 1 and 2) which reached steady levels within 60–80 minutes. This increase in mucosal blood flow was only seen at high acid concentrations, when acid back-diffusion occurred (Figure 1), and was therefore not due to a direct action of taurocholate on the mucosa.

In a further three experiments where either the concentration of acid (60–120 mM HCl) or taurocholate (2–10 mM) was varied, the changes in acid back-diffusion were accompanied by corresponding changes in mucosal blood flow and there appeared to be a direct relationship between these parameters.

Effects of taurocholate and indomethacin on mucosal blood flow

In four experiments, when steady rates of mucosal blood flow and acid-loss were obtained during perfusion of taurocholate (2 mM) and acid (100 mM HCl), indomethacin (20 mg/kg, i.v.) was administered (Figure 2). Although there was no marked change in acid-loss, a significant decrease in the mucosal blood flow was observed ($P<0.01$ after 40 minutes). The effect of indomethacin and taurocholate on mucosal blood flow and acid-loss are shown in Figure 3.

Effects of a prostaglandin methyl analogue

Subcutaneous injections of (15S)-15 methyl prostaglandin E_2 methyl ester (5 μg/kg every hour) from the start of taurocholate (2 mM) and indomethacin administration (20 mg/kg, s.c.) during acid perfusion (100 mM HCl) caused a significant ($P<0.02$)

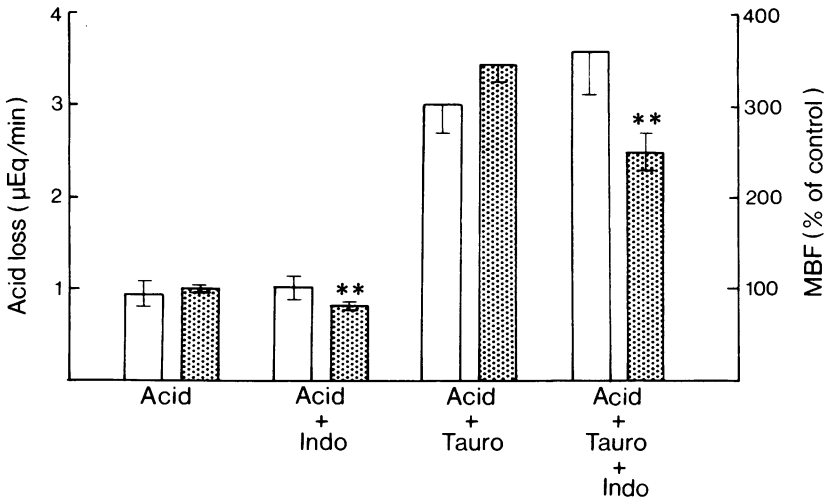

Figure 3 Summary of the changes in acid back-diffusion (open columns) and mucosal blood flow (MBF, stippled columns) during gastric perfusion of acid saline (HCl, 100 mM). Results, expressed as the mean are the values 1 h after administration of either indomethacin (Indo, 20 mg/kg i.v.) in four experiments, or successive treatments with taurocholate (Tauro, 2 mM) and indomethacin (20 mg/kg, i.v.) in a further four experiments. Vertical lines show s.e. mean.

reduction in the erosion index observed after 3 h (from 6.5 ± 0.4 to 2.9 ± 0.5). The overall acid-loss during this 3 h perfusion period was also significantly reduced from 458 ± 39 μEq/3 h ($n=5$) to 345 ± 25 μEq/3 h ($n=4$; $P<0.02$).

In eight other experiments with indomethacin (20 mg/kg, s.c.) and taurochlolate (2 mM)-administration during 60 mM HCl perfusion, the 3 h-erosion index was reduced from 3.9 ± 0.3 to 1.0 ± 0.4, and the acid loss from 262 ± 9 to 206 ± 16 μEq/3 h ($n=4$ for each group; $P<0.01$) by concurrent administration of the (15S)-15 methyl prostaglandin E_2 analogue (5 μg kg^{-1} h^{-1}, s.c.).

In further experiments, the effects of intravenous infusion of (15S)-15 methyl prostaglandin E_2 on mucosal blood flow and p.d. were determined during acid (100 mM HCl) perfusion. When steady rates of mucosal blood flow were obtained, 1.5 h following indomethacin administration, infusion of (15S)-15 methyl E_2 (5 μg kg^{-1} h^{-1}) caused a gradual increase in p.d. (by 7.1 ± 1.5 mV after 1 h, $n=5$), and an increase in mucosal blood flow (by 38.3 ± 7.3% of control after 1 h, $n=5$). In three other experiments during concurrent acid-taurocholate perfusion, this dose of the prostaglandin analogue likewise increased mucosal blood flow (by 40 ± 8% of control) and p.d. (by 5.2 ± 0.6 mV).

During acid perfusion alone, an increase in p.d. (8 mV, 1 experiment) was observed following the prostaglandin infusion; in three experiments, initial single intravenous injections of (15S)-15 methyl E_2 (2.5 μg/kg) also increased the resting p.d. (by 8.7 ± 0.9 mV after 30 min, $n=3$) although subsequent repeated injections gave variable results (a fall in p.d. was often observed).

Discussion

The reflux of bile into the gastric lumen has been considered as a possible factor in the aetiology of peptic ulceration (Du Plessis, 1965) and in the pathogenesis of the gastric erosions induced by non-steroid anti-inflammatory agents (Djahanguiri, Abtahi & Hemmati, 1973; Semple & Russell, 1975). Bile, by virtue of its surface-active properties, is thought to damage the gastric mucosa by promoting the back-diffusion of hydrogen-ions from the lumen across the mucosa (Davenport, 1968). However, in the present study the increase in acid back-diffusion with the bile salt, taurocholate, in acid solution did not lead to marked mucosal damage. It is therefore possible that the accompanying rise in gastric mucosal blood flow is a protective mechanism preventing the excessive accumulation of acid within the mucosa under such pathological conditions. This is supported by the finding that indomethacin, in doses which reduced this hyperaemic response to taurocholate perfusion, caused a marked potentiation of erosion formation.

An increase in mucosal blood flow, measured by aminopyrine clearance, has also been observed in the exteriorized, chambered preparation of canine fundic

segments, using concentrations of taurocholate (5 mM) in acid solution in the same range as those in the present study (Ritchie, 1975). In a similar preparation, a high concentration of taurocholate (40 mM), which induced a ten-fold increase in acid back-diffusion with gross mucosal damage, also increased mucosal blood flow as measured by microspheres (Cheung, Moody & Reese, 1975). However, in that study aminopyrine clearance failed to show any marked change, and the authors suggested that this latter technique had limitations under such conditions of extensive mucosal damage. Although we have used a similar clearance technique to estimate changes in rat mucosal blood flow, the results were obtained at the early stages of erosion formation or with only slight mucosal damage. It is not known whether such mucosal damage could explain the divergent results of O'Brien & Silen (1973), who found that high concentrations of taurocholate (10–40 mM) caused a decrease in aminopyrine clearance. This action, observed even in the absence of acid back-diffusion, suggests some direct effect of the bile-salt preparation used in their study and contrasts with the present study where taurocholate had no direct effect on mucosal blood flow independent of acid back-diffusion. The bulk of the evidence in the dog, therefore, agrees with the present findings in the rat that acid back-diffusion can lead to an increase in mucosal blood flow. The mechanism by which this mucosal hyperaemia occurs is not known, but it may be a direct response of the mucosal microvasculature to the increased acid back-diffusion, or to the local release of mediators, possibly a prostaglandin.

The fall in gastric mucosal blood flow induced by indomethacin, in doses sufficient to inhibit postaglandin formation (Vane, 1971) in the mucosa (Main & Whittle, 1975a) could suggest a role for endogenous prostaglandins (or some other product of the prostaglandin cyclo-oxygenase system) in the local regulation of the gastric microcirculation; it has been found that primary prostaglandins of the E and A series for example, can increase resting mucosal blood flow (Main & Whittle, 1973b). Whether the reduced local blood flow with indomethacin is solely the consequence of a reduction in a prostaglandin-mediated vasodilator tone is not known. It is possible that cyclo-oxygenase inhibition by indomethacin leads to the production of vasoconstrictor metabolites from prostaglandin precursors, or that indomethacin has inherent vasoconstrictor activity. The greater activity of indomethacin on taurocholate-elevated mucosal blood flow could also suggest that microcirculatory regulation by the prostaglandin-system is of more importance under patho-physiological conditions.

Although these studies can give an indication of the gross changes in the local microcirculation, the measurement of mucosal blood flow by the techniques currently available can give only limited information about microvascular events at the localized sites of erosion formation. Small overall changes could therefore reflect intense focal ischaemia and such areas would be likely to be the sites of subsequent erosions, especially in the presence of other noxious stimuli, such as acid.

The failure of indomethacin, administered systemically, to alter either p.d., which can give an indication of mucosal hydrogen- or sodium-ion flux, or the acid back-diffusion, may argue against a local role for endogenous prostaglandins in the maintenance of the rat mucosal 'barrier'. However, intragastric administration of several non-steroid, anti-inflammatory agents including indomethacin, has previously been demonstrated to promote acid-loss and changes in p.d. in the dog (Chvasta & Cooke, 1972). Although this could reflect a species difference, a more likely explanation is that such drugs have a topical action, perhaps of a physico-chemical nature, unrelated to inhibition of local prostaglandin synthesis. The possible effects of these aspirin-like drugs on gastric mucosal blood flow are therefore complex with both direct effects and those as a consequence of acid back-diffusion, and the observed actions could well depend on the dose and route of administration. Furthermore, any hyperaemic response to acid back-diffusion caused by these aspirin-like drugs may be attenuated by their concurrent direct effects on the microvasculature. Thus, the potency of non-steroid, anti-inflammatory agents in causing either or both actions may give a good indication of the ability of such drugs to cause gastric erosions.

These results in the rat suggest that, whereas a reduction in mucosal blood flow, as seen with indomethacin, or an increase in acid back-diffusion, as observed with taurocholate, can lead to a low incidence of erosions, a combination of both agents and both actions produces extensive mucosal damage. A similar conclusion regarding the effects of mucosal ischaemia and acid back-diffusion was reached from studies on the dog mucosa (Ritchie, 1975), which showed that, whereas the reduction in mucosal blood flow with vasopressin alone did not produce erosions, the mucosal damage with taurocholate in acid solution was potentiated. It is also of interest that in an early study on the dog, haemorrhagic shock (which could reduce gastric blood flow) produced mucosal lesions only in the presence of both acid test-solution and bile-salts (Safaie-Shirazi, Denbesten & Hamza, 1972).

A 15-methyl analogue of prostaglandin E_2 was previously found to inhibit the gastric erosions induced by taurocholate and a non-steroid anti-inflammatory agent in the rat (Carmichael *et al.*, 1976). However, in that study the prevention of mucosal damage by intragastric administration of the (15R)-epimer, which could be converted to the potent gastric antisecretory (15S)-epimer in the acid environment (see Main & Whittle, 1975b), is likely to be the consequence of inhibition of the gastric acid

secretion (Whittle, 1976a). The ability of the (15S)-methyl prostaglandin E_2 analogue to inhibit erosion formation in the presence of exogenous perfused acid (Whittle, 1976a) suggests further protective mechanisms of the prostaglandins on the mucosa.

The observation that the prostaglandin methyl analogue reduced the acid loss provoked by taurocholate supports the findings in the dog that the analogue can reduce the acid back-diffusion following intragastric administration of aspirin and indomethacin (Cohen, 1976). Furthermore, this prostaglandin analogue also increased rat mucosal blood flow under conditions of taurocholate and indomethacin administration, as shown previously under resting conditions (Main & Whittle, 1975b). It is likely that such actions on the mucosal permeability to acid (or other ions), coupled with the observed changes in mucosal blood flow are important factors in the process by which prostaglandins prevent gastric mucosal damage.

This work was supported by a grant to Professor G.P. Lewis from the M.R.C. Prostaglandins were kindly supplied by the Upjohn Company, Kalamazoo, U.S.A.

References

ABTAHI, F.S. & DJAHANGUIRI, B. (1975). Decreased incidence of indomethacin-induced gastric ulceration in rats by bile duct diversion. *Br. J. Surg.*, **62**, 113–114.

CARMICHAEL, H.A., NELSON, L., RUSSELL, R.I., CHANDRA, V., LYON, A. & COCHRAN, K.M. (1976). Effect of prostaglandin (15R) 15 methyl-E_2 methyl ester on aspirin and taurocholic acid-induced gastric mucosal haemorrhage in rats. *Gut*, **17**, 33–36.

CHEUNG, L.Y., MOODY, F.G. & REESE, R.S. (1975). Effect of aspirin, bile salt and ethanol on canine gastric mucosal blood flow. *Surgery*, **77**, 786–792.

CHVASTA, T.E. & COOKE, A.R. (1972). The effect of several ulcerogenic drugs on the canine gastric mucosal barrier. *J. lab. clin. Med.*, **79**, 302–315.

COHEN, M.M. (1976). 15-Methyl prostaglandin E_2 protects gastric mucosal barrier. In *Advances in Prostaglandin and Thromboxane Research*, Vol. 2, ed. Samuelsson, B. & Paoletti, R. pp. 937–938. New York: Raven Press.

DAVENPORT, D.W. (1968). Destruction of the gastric mucosal barrier by detergents and urea. *Gastroenterology*, **54**, 175–181.

DJAHANGUIRI, B., ABTAHI, F.S. & HEMMATI, M. (1973). Prevention of aspirin-induced gastric ulceration by bile-duct or pylorus ligation in the rat. *Gastroenterology*, **65**, 630–633.

DU PLESSIS, D.J. (1965). Pathogenesis of gastric ulceration. *Lancet*, **i**, 974–978.

MAIN, I.H.M. & WHITTLE, B.J.R. (1973a). Gastric mucosal blood flow during pentagastrin- and histamine-stimulated acid secretion in the rat. *Br. J. Pharmac.*, **49**, 534–542.

MAIN, I.H.M. & WHITTLE, B.J.R. (1973b). The effects of E and A prostaglandins on gastric mucosal blood flow and acid secretion in the rat. *Br. J. Pharmac.* **49**, 428–436.

MAIN, I.H.M. & WHITTLE, B.J.R. (1975a). Investigation of the vasodilator and antisecretory role of prostaglandins in the rat gastric mucosa by use of non-steroidal anti-inflammatory drugs. *Br. J. Pharmac.*, **53**, 217–224.

MAIN, I.H.M. & WHITTLE, B.J.R. (1975b). Potency and selectivity of methyl analogues of prostaglandin E_2 on rat gastrointestinal function. *Br. J. Pharmac.*, **54**, 309–317.

O'BRIEN, P. & SILEN, W. (1973). Effect of bile salts and aspirin on the gastric mucosal blood flow. *Gastroenterology*, **64**, 246–253.

RITCHIE, W.P. (1975). Acute gastric mucosal damage induced by bile salts, acid and ischaemia. *Gastroenterology*, **68**, 699–707.

SAFAIE-SHIRAZI, S., DENBESTEN, L. & HAMZA, K.N. (1972). Absorption of bile salts from the gastric mucosa during hemorrhagic shock. *Proc. Soc. exp. Biol. Med.*, **140**, 924–927.

SEMPLE, P.F. & RUSSELL, R.I. (1975). Role of bile acids in the pathogenesis of aspirin-induced gastric mucosal haemorrhage in rats. *Gastroenterology*, **68**, 67–70.

VANE, J.R. (1971). Inhibition of prostaglandin synthesis as a mechanism of action of aspirin-like drugs. *Nature, New Biol.*, **231**, 232–235.

WHITTLE, B.J.R. (1975). Gastric acidity and the mechanisms by which prostaglandins prevent indomethacin-induced gastric erosions. *Br. J. Pharmac.*, **55**, 242–243P.

WHITTLE, B.J.R. (1976a). Relationship between the prevention of rat gastric erosions and the inhibition of acid secretion by prostaglandins. *Eur. J. Pharmac.*, **40**, 233–239.

WHITTLE, B.J.R. (1976b). Prostaglandins and changes in the gastric mucosal barrier and blood flow during indomethacin- and bile salt-induced mucosal damage. *Br. J. Pharmac.*, **56**, 340–341P.

(Received December 23, 1976. Revised February 10, 1977.)