and 30 Hz respectively. These relaxations seemed to be mostly due to the stimulation of adrenergic nerve, since they were almost completely abolished by tetrodotoxin (5×10^{-7}M) or guanethidine (5×10^{-6}M). Morphine at less than 1×10^{-6}M did not depress the elicited relaxation (Fig. 1a). At a higher dose (1×10^{-5}M), the drug did not inhibit the relaxation elicited with 5 Hz, rather it was potentiated slightly (Fig. 2). This potentiation may be caused by inhibition of neuronal uptake of transmitter (Starke, 1977). Transmural stimulation in the presence of guanethidine (5×10^{-6}M) elicited only relaxation which was abolished by tetrodotoxin (5×10^{-7}M).

It is suggested that the relaxation elicited is mainly due to the stimulation of non-adrenergic inhibitory nerves. Morphine reversibly dose-dependently depressed these elicited relaxations (Fig. 1b). This inhibitory effect of morphine varied inversely with stimulus frequency (Fig. 2). At 0·5 Hz for 4 s, the drug inhibited the elicited response by about 60% while at 10 Hz its action was negligible (Fig. 2). Naloxone (1×10^{-6}M), a pure opiate antagonist (Kosterlitz & Watt, 1968), almost completely reversed the inhibition of morphine (Fig, 1b).

In conclusion, morphine (1×10^{-8}—1×10^{-6}M) has no inhibitory effect on the adrenergic inhibitory response of the taenia to perivascular stimulation. On the other hand, it depresses the non-adrenergic inhibitory response of the taenia to transmural stimulation via activation of opiate receptors probably located in the myenteric plexus of the taenia. The depression is negatively correlated with the frequency of nerve stimulation.

June 15, 1978

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The relative activity of prostacyclin (PGI_2) and a stable analogue 6β-PGI_1 on the gastrointestinal and cardiovascular systems

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Prostacyclin (PGI_2), a major product of arachidonic acid metabolism in vascular tissue, is a potent but unstable vasodilator and inhibitor of platelet aggregation (Moncada, Gryglewski & others, 1976). More recently, prostacyclin has been shown to be generated by the gastric mucosa of several species (Moncada, Salmon & others, 1978), and to be a potent inhibitor of gastric acid secretion and erosion formation in the gastric mucosa of the rat (Whittle, Boughton-Smith & others, 1978). We now describe the activity of a stable 5-6-dihydro prostacyclin, 6β-PGI_1 (Johnson, Lincoln & others, 1977) on some aspects of gastrointestinal function and the cardiovascular system.

Inhibition of gastric acid secretion and concomitant changes in systemic arterial blood pressure in the urethane-anaesthetized rat were determined as previously described (Main & Whittle, 1973). During steady submaximal rates of acid secretion induced by pentagastrin (0·5 μg kg^{-1} min^{-1}, i.v.), prostacyclin, its chemical decomposition product, 6-oxo-$PGF_{1\alpha}$ (Johnson & others, 1976) or 6β-PGI_1, each dissolved in an isotonic sodium bicarbonate solution (1·25% w/v; pH 8·6; 0°) were infused intravenously. The fall in acid output, which reached stable levels within 30 min was expressed as % inhibition of the control secretory values (1·5–2·5 μequiv min^{-1}). As is shown in Fig. 1, the stable analogue was some 16 times less potent than prostacyclin on intravenous infusion. Like prostacyclin, 6β-PGI_1 lowered systemic arterial blood pressure (BP) (Fig. 1). For doses inhibiting acid output by 50% (ID50), 6-oxo-$PGF_{1\alpha}$ and prostacyclin have similar relative activities in inhibiting gastric acid secretion and in reducing BP, whereas the analogue was relatively more active as an antisecretory agent (Table 1). Thus, the stable analogue shows some selectivity of action towards the gastric antisecretory actions but away from the cardiovascular actions of prostacyclin.

In the studies on the isolated lumen-perfused whole-stomach of the immature (30–50 g) rat (Bunce & Parsons, 1976), prostaglandins were added to the

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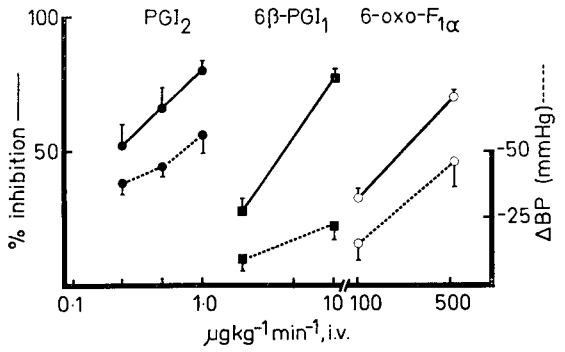

FIG. 1. Inhibition of pentagastrin (0·5 μg kg^{-1} min^{-1})-stimulated acid secretion and the fall in systemic arterial blood pressure (BP) induced by prostacyclin (PGI_2), 6-oxo-$PGF_{1\alpha}$ and 6β-PGI_1 in the anaesthetized rat. Results are shown as mean ± s.e. mean of 3–5 values.

serosal solution (pH 7·6; 37°) during stable rates of histamine- (20 μg ml^{-1}) stimulated acid output (Whittle & others, 1978). Prostacyclin (1 μg ml^{-1}) inhibited acid output by 37 ± 12% (n = 3) whereas 6β-PGI_1 (1 μg ml^{-1}) inhibited acid output by 71 ± 9% (n = 4), maximal effects being obtained 15–30 min after administration. From a further 10 experiments using prostacyclin (0·5–5 μg ml^{-1}) and 6β-PGI_1 (0·5–2 μg ml^{-1}) the ID50 for prostacyclin was 2·2 μg ml^{-1} whereas the ID50 for 6β-PGI_1 was 0·31 μg ml^{-1} (Table 1).

Prostacyclin has previously been shown to inhibit gastric erosions (Whittle & others, 1978), In the present work, the incidence and severity of gastric mucosal erosions formed in glandular mucosa 3 h after administration of indomethacin (20 mg kg^{-1}, s.c.) was assessed as previously described (Whittle, 1976). Indomethacin (10 mg ml^{-1}) was dissolved in 5% $NaHCO_3$ solution immediately before use. The results were expressed as % inhibition of the control erosion index (Table 2). The ID50 for prostacyclin was 350 μg kg^{-1}, s.c. and 250 μg kg^{-1}, s.c. for 6β-PGI_1. The C6-epimer, 6α-PGI_1 was less active (ID50, 500 μg kg^{-1}, s.c.) as an inhibitor of erosions, as shown in Tables 2 and 3.

In four experiments on the rat superfused stomach-strip preparation (Vane, 1957), prostacyclin was approx. 1·3 times more active than 6β-PGI_1 in contracting this tissue (recorded with isotonic transducers) and approx. 2·8 times more active than 6α-PGI_1 (Table 3).

The activity of the prostacyclin analogues as inhibitors of human platelet aggregation was also investigated. Blood was freshly collected into trisodium citrate (3·15% w/v; 0·1 vol.) and centrifuged (200 *g* for 15 min). Inhibition of platelet aggregation was determined in a

Table 1. *Inhibition of rat gastric acid secretion* in vitro *and* in vivo *by prostacyclin (PGI_2), its decomposition product 6-oxo-$PGF_{1\alpha}$ and a stable analogue, 6β-PGI_1.* The results, which are doses required to inhibit by 50% (ID50) the gastric acid secretion from rat perfused stomach stimulated by histamine *in vitro*, and by pentagastrin *in vivo*, and the fall in systemic arterial blood pressure at these doses, are from 3–5 experiments.

	In vitro ID50 (μg ml^{-1})	*In vivo* ID50 (μg kg^{-1} min^{-1})	ΔBP (mm Hg)
PGI_2	2·2	0.25	−40
6-oxo-$PGF_{1\alpha}$	>100	350	−33
6β-PGI_1	0·3	4·0	−14

Table 2. *Inhibition of indomethacin-induced rat gastric erosions.* Indomethacin (20 mg kg^{-1}, s.c.) was injected immediately before the subcutaneous administration of the prostaglandins, and the erosion index was assessed after 3 h. Results, expressed as % inhibition of the control erosion index, are shown as mean ± s.e. mean of (n) values.

	Dose (μg kg)	% Inhibition	(n)
PGI_2	250	25 ± 8	(18)
	500	68 ± 10	(18)
6β-PGI_1	125	23 ± 15	(30)
	250	50 ± 14	(30)
6α-PGI_1	500	46 ± 20	(10)
6-oxo-$PGF_{1\alpha}$	500	12 ± 9	(18)
PGE_2	125	41 ± 17	(18)
	500	69 ± 5	(68)

Table 3. *Relative potency of the epimers 6α-PGI_1 and 6β-PGI_1 compared with prostacyclin (PGI_2).* Relative potencies were calculated from dose producing 50% of maximal responses. Inhibition of ADP-induced human platelet aggregation was determined after 1 min incubation (37°) of platelet-rich plasma with the prostaglandins. Inhibition of indomethacin (20 mg kg^{-1}, s.c.)-induced gastric erosions was determined 3 h after administration. Contractions of the isolated superfused rat stomach strip were recorded via isotonic transducers. Results, expressed as mean ± s.e. mean, are from 3–5 experiments.

	PGI_2	6β-PGI_1	6α-PGI_1	*Ratio* 6β : 6α-PGI_1
Human platelet aggregation	1	0·005 ±0·001	0·001 ±0·0003	1 : 0·25
Rat gastric erosions	1	1·7 ±0·3	0·8 ±0·1	1 : 0·5
Rat stomach strip	1	0·75 ±0·05	0·36 ±0·04	1 : 0·5

Born-type aggregometer by incubating aliquots (0·5 ml) of the platelet-rich plasma (PRP) with the prostaglandin for 1 min before the addition of sufficient adenosine diphosphate (ADP, 0·5–2 μM) to cause the second phase of platelet aggregation. In five experiments, the ID50 for the analogue, 6β-PGI$_1$ was 116 $\pm$ 20 ng ml^{-1} and thus was 250 times less active as an inhibitor in human PRP than prostacyclin (ID50, 0·5 $\pm$ 0·07 ng ml^{-1}). The finding that the epimer, 6α-PGI$_1$, was some 3–4 times less active than 6β-PGI$_1$ (ID50 350 $\pm$ 30 ng ml^{-1}) contrasts with the report by Tonga, Gandolfi & others (1977) suggesting that the 6α-epimer was the more active of the pair. Whether this discrepancy is the result of different stereochemical assignment, separation and purity of the compounds synthesized in the different laboratories, or some other experimental factor, remains to be resolved.

The present results indicate that although the stable analogue 6β-PGI$_1$ shares several of the properties of prostacyclin, its relative potency to prostacyclin depends on the system investigated. The analogue was less potent as a vasodilator and inhibitor of human platelet aggregation. Like prostacyclin the analogue inhibited the formation of mucosal erosions and also acid secretion in the rat stomach *in vivo* and *in vitro*. In the *in vivo* preparation where prostacyclin and the analogue were infused intravenously, prostacyclin was more potent as an antisecretory agents. However, following subcutaneous administration in the 3 h erosion study, the analogue was more active. Furthermore, in the *in vitro* isolated perfused stomach preparation, in which the prostaglandins require some 15–30 min to elicit a full response, the analogue was the more potent, presumably reflecting the rapid breakdown of prostacyclin under the incubation conditions. In the other *in vitro* systems where prolonged incubation was not required to achieve the maximal response, prostacyclin was the more potent, as an inhibitor of platelet aggregation and in contracting the rat stomach strip. Thus, although the stable analogue 6β-PGI$_1$ may be only a weak agonist for prostacyclin-sensitive sites, its relative potency to prostacyclin is greatly enhanced under conditions where stability is of importance.

July 12, 1978

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Action of chloroquine on pleurisy due to *Bordetella pertussis* hypersensitivity

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It is now generally agreed that chloroquine has a good effect on rheumatoid polyarthritis. On the contrary, its actions in the usual phamacological models of experimental inflammation (review by Swingle, 1974) are limited. We describe here its action on delayed *Bordetella pertussis* hypersensitivity in rats.

We have modified the technique previously described (Tarayre, Delhon & Lauressergues, 1977) in order to shorten duration of the sensitization period. Sprague Dawley male rats, 280–320 g, were used. *B. pertussis* suspension (Institut Pasteur—5 $\times$ 10^9 killed organisms ml^{-1}) was homogeneously mixed (v/v: 50/50) with Freund's complete adjuvant (Difco). 0·2 ml of this mixture was injected intramuscularly into both thighs of rats. 6 days later, 0·1 ml of *B. pertussis*-suspension was injected into the pleural cavity. 48 h later, the pleural exudate was taken and measured, and leucocytes counted with a Coulter Counter. After the cells had been spread on slides, the number of mononuclear and polynuclear cells was counted. In a first series of experiments, chloroquine diphosphate was given around the time of challenge (4 administrations of 10 mg kg^{-1}, orally). In a second series, the compound was given from the day of sensitization and during the duration of the experiment (9 administrations of 10 mg kg^{-1},

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