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Response of the human cardiac sphincter to circulating prostaglandins $F_{2\alpha}$ and E_2 and to anti-inflammatory drugs

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SUMMARY The effects on intraluminal pressure in the oesophagus, the cardiac sphincter, and the gastric fundus of intravenous prostaglandin $F_{2\alpha}$, E_2, and of rectal indomethacin were studied in 41 subjects. Intravenous infusion of prostaglandin $F_{2\alpha}$ (0·05 to 0·8 μg kg^{-1} min^{-1}) produced marked, dose-related and sustained elevation of cardiac sphincter pressure without significantly affecting oesophageal peristalsis or gastric fundal motility. Sphincteric relaxation during swallowing was prolonged. Plasma gastrin levels were unchanged. Intravenous infusion of PGE_2 (0·08 μg kg^{-1} min^{-1}) inhibited sphincter contractions to serial bolus intravenous injections of pentagastrin (0·1 or 0·2 μg kg^{-1}). Rectal indomethacin (200 mg) resulted in a rise of cardiac sphincter pressure, suggesting that endogenous synthesis of an inhibitory (E-type) prostaglandin was suppressed. The results indicate that prostaglandin E_2 may be concerned in the regulation of cardiac sphincter tone in man, whilst prostaglandin $F_{2\alpha}$ may be useful in the treatment of gastrooesophageal reflux.

Pressure level in the cardiac sphincter plays a part in the prevention of gastrooesophageal reflux and depends upon the tone of circular oesophageal muscle in that area. The neural and humoral control of sphincteric tone is not completely understood. Human alimentary muscle is highly sensitive to prostaglandins (PGs): *in vitro* PGE_2 produces relaxations and $PGF_{2\alpha}$ contractions of the circular muscle layer (Bennett, Murray, and Wyllie, 1968; Bennett, Eley, and Scholes, 1968; Bennett and Posner, 1971). Prostaglandin E_2 occurs naturally in the human gastric mucosa (Bennett, Stamford, and Unger, 1972). We have recorded motor responses of the human gastrooesophageal junction to intravenous $PGF_{2\alpha}$ and PGE_2. The effects on cardiac sphincteric pressure of rectally administered indomethacin have also been studied.

Methods and Subjects

Intraluminal pressures were measured with a four-lumen tube assembly in the oesophagus, the cardiac sphincter, and the gastric fundus of fasting male subjects reclining in the supine position. The four lumens had side-opening tips 5 cm apart and were perfused with distilled water at a constant rate of 7 μl sec^{-1}. After intubation the tube assembly was withdrawn in a stepwise fashion until one of the tips was in the cardiac sphincter, which was identified as a zone of high pressure with reflex relaxations to swallowing. In most studies the tube was positioned so that the two proximal tips were in the oesophagus, the third in the sphincter and the most distal tip in the fundus: in a few subjects the most proximal or the second tip was placed in the sphincter. Once the sphincter was identified the tube was finely adjusted until the highest pressure was recorded. The tube assembly was then securely taped to the side of the nose. Swallowing was monitored with a pneumograph placed snugly around the larynx. All the pressures were recorded on a multichannel pen writer (Devices).

Fifty-five subjects were studied: seven were normal volunteers and 48 were patients with upper abdominal complaints related to peptic ulceration or to symptoms of gastrooesophageal reflux: patients with hiatus hernia were excluded. All gave their informed consent to the test which was approved by the Central Middlesex Hospital Ethical Commit-

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tee. After intubation and positioning of the tube, basal sphincteric pressures were recorded for a 20- to 30-min control period. Only subjects with stable sphincter pressures during this period were accepted for the study. Each subject was studied on one occasion only.

Four variables of intraluminal pressures were measured on the pressure records by two observers working together. (1) The cardiac sphincter pressure was measured at end-expiratory level during each consecutive minute of the test, taking the simultaneously recorded gastric fundal pressure as zero: the results were pooled in five-min periods and averaged; (2) the depth and duration of sphincteric relaxations during swallowing; (3) the amplitude of oesophageal peristaltic contractions; and (4) the duration and amplitude of the fundal pressure waves were also measured.

Bolus injections of drugs or 0·15M saline were made into an intravenous drip. Intravenous infusions of PGs were administered at a constant rate from syringes driven by a syringe pump and were preceded and followed by similarly administered 0·15M saline. Venous blood for plasma gastrin estimations by radioimmunoassay was drawn from the contralateral arm before drugs were injected and at the time of maximal response to them. Student's paired t test was used for calculations of statistical significance, which were performed on groups receiving the same dose of prostaglandin.

Results

Fourteen subjects (three normal, 11 patients) had unstable basal cardiac sphincter pressure records and the studies were therefore abandoned. The decision not to proceed with these studies was based solely on the instability, and not on the amplitude, of the sphincteric pressures. The subjects eliminated had a wide range of sphincter pressures. The unstable pressures were due in some instances to frequent swallowing by subjects with sensitive nares or pharynx who tolerated the tube badly: in others no reason for variations in sphincteric pressure was apparent. Results in 41 subjects were available for analysis. All these tolerated the test well and experienced no unwanted effects, apart from transient erythema at the site of the infusion of prostaglandin E_2.

BOLUS INJECTION OF $PGF_{2\alpha}$

Bolus injections of $PGF_{2\alpha}$ at 0·0, 2·5, 5·0, 10·0, or 40 $\mu g\ kg^{-1}$ administered over 15 sec were given to seven subjects according to a Latin square pattern, but no effect on cardiac sphincter pressures was observed (table IV).

INTRAVENOUS INFUSION OF $PGF_{2\alpha}$

Intravenous infusions of $PGF_{2\alpha}$ at 0·05, 0·1, 0·2, 0·4, or 0·8 $\mu g\ kg^{-1}\ min^{-1}$ administered for 20 min to 15 subjects resulted in marked and sustained increase of cardiac sphincteric pressures. The sphincter pressures began to rise approximately 10 min after the start and persisted for 15 to 20 min after the end of $PGF_{2\alpha}$ infusion (table I, fig 1). The response was clearly related to the dose, although a classical sigmoid dose-response curve was not obtained (fig 2). The relaxations of the cardiac sphincter to swallowing were not impaired even at the height of the response, but on the contrary, the duration of sphincteric relaxation was prolonged during maximal increase of sphincter

Subject	*Dose of $PGF_{2\alpha}$ ($\mu g\ kg^{-1}\ min^{-1}$ × 20 min)*	*Cardiac Sphincter Pressures (mm Hg)*		*Plasma Gastrin (pg ml^{-1})*	
		Mean Basal[1] (±SEM)	*Maximal[2] Pressure*	*Basal*	*During Maximal Pressure*
1	0·05	15·8±0·6	25·4	—	—
2	0·05	19·0±1·0	20·4	—	—
3	0·05	4·0±0·7	10·8	—	—
4	0·1	21·7±3·4	43·8	—	—
5	0·1	23·8±1·1	48·2	—	—
6	0·2	11·5±1·0	30·7	—	—
7	0·2	12·0±0·6	33·3	—	—
8	0·2	13·0±0·6	39·4	—	—
9	0·4	17·3±2·8	41·5	16	14
10	0·4	15·1±2·1	26·0	14	22
11	0·4	28·6±3·1	49·1	—	—
12	0·8	5·0±0·5	45·3	20	14
13	0·8	13·6±1·0	49·7	6	6
14	0·8	13·1±2·0	73·0	32	30
15	0·8	12·4±0·3	51·5	10	8

Table I *Effect of $PGF_{2\alpha}$ on cardiac sphincter pressures*

[1]Mean basal pressure = average of four consecutive five min periods immediately preceding infusion of $PGF_{2\alpha}$, ± standard error of mean.
[2]Maximal pressure = highest pressure recorded during any five min period following the infusion of $PGF_{2\alpha}$.

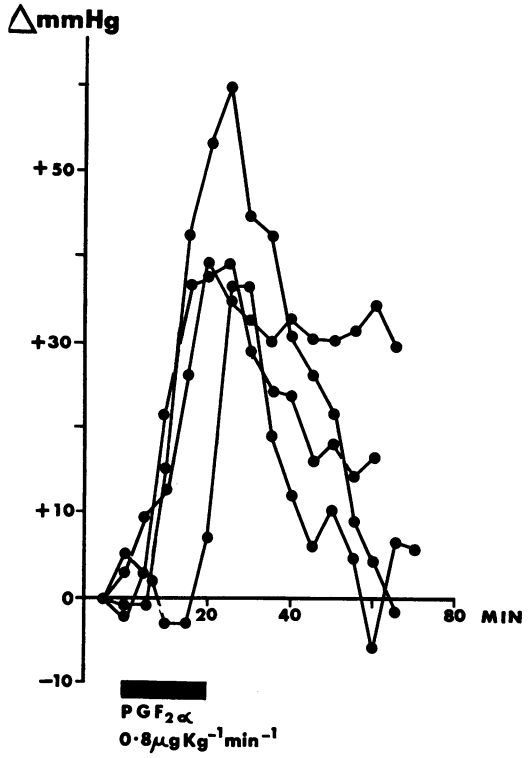

Fig 1 *Increases in cardiac sphincter pressure (four subjects) in response to intravenous $PGF_{2\alpha}$ 0·8 μg kg^{-1} min^{-1}. Zero level = mean basal pressure.*

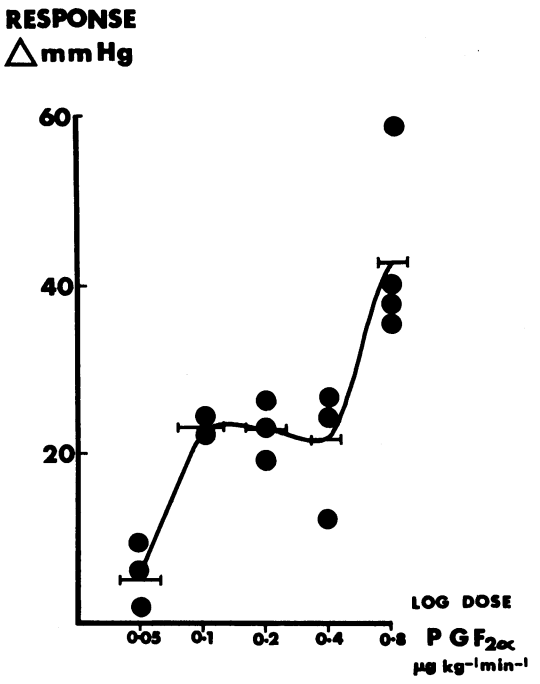

Fig 2 *Dose-response curve of cardiac sphincter pressure to various doses of prostaglandin $F_{2\alpha}$.*

pressure produced by prostaglandin $F_{2\alpha}$. The prolonged relaxation was observed in 12 of the 13 studies in which measurement of this variable was feasible, the effect being significant in the four subjects given $PGF_{2\alpha}$ 0·8 μg kg^{-1} min^{-1} ($P < 0.01$, table II).

Dose of $PGF_{2\alpha}$ (μg kg^{-1} min^{-1})	*Relaxation Time (sec) of Lower Oesophageal Sphincter during Swallowing*	
	Control	*After $PGF_{2\alpha}$*
0·5	8·9	11·4
0·1	12·9	19·5
0·1	12·6	14·6
0·2	9·7	9·2
0·2	6·0	9·4
0·2	13·9	19·5
0·4	13·5	16·0
0·4	12·0	15·5
0·4	12·0	15·0
0·8	7·8	13·0
0·8	9·2	15·4
0·8	9·9	22·0
0·8	7·8	12·5

Table II *Effect of $PGF_{2\alpha}$ on sphincteric relaxation to swallowing*[1]

[1]Values are averages of relaxations due to spontaneous swallowing during the control period and during the five-min period coinciding with maximal response to PG, respectively.

The amplitude of oesophageal peristaltic waves increased in 11 of 12 subjects at the time of maximal response of the sphincter to $PGF_{2\alpha}$, but the difference from basal values was not significant at the highest dose level ($P = 0.1$, table III). Gastric fundal pressure activity was unaffected. Plasma gastrin levels measured in six subjects before $PGF_{2\alpha}$ and during maximal sphincteric response were unaltered (table I).

INTRAVENOUS INFUSION OF PGE_2

Intravenous infusions of PGE_2 at 0·01, 0·02, 0·04, and 0·08 μg kg^{-1} min^{-1} administered for 20 min in nine subjects had no effect on any variable of intraluminal pressure (table IV).

INTRAVENOUS INFUSIONS OF PGE_2 AND BOLUS INJECTIONS OF PENTAGASTRIN

Serial bolus intravenous injections of pentagastrin (0·1 or 0·2 μg kg^{-1} every 10 min given over 15 sec) were given to three subjects and resulted in reproducible contractions of the cardiac sphincter. Prostaglandin E_2 0·08 μg kg^{-1} min^{-1} infused for 20 min partially inhibited the sphincteric responses to pentagastrin in two subjects: in the third no

Dose of $PGF_{2\alpha}$ ($\mu g\ kg^{-1}\ min^{-1}$)	Amplitude (mm Hg) of Oesophageal Peristaltic Waves			
	10 cm Proximal to Sphincter		5 cm Proximal to Sphincter	
	Control	After $PGF_{2\alpha}$	Control	After $PGF_{2\alpha}$
0·1	26·3	38·3	55·4	71·7
0·1	34·0	45·8	51·8	78·5
0·2	30·7	37·0	45·6	54·8
0·2	38·7	38·7	48·1	51·4
0·2	23·7	27·3	27·7	29·2
0·4	30·3	55·4	18·3	27·2
0·4	34·8	52·5	38·0	50·8
0·4	15·1	20·9	17·2	36·5
0·8	25·6	42·3	38·0	56·1
0·8	15·0	20·7	25·6	27·0
0·8	17·2	23·1	48·2	52·0
0·8	50·37	15·8	25·9	32·7

Table III *Effect of $PGF_{2\alpha}$ on amplitude of oesophageal peristaltic waves*[1]

[1]Data collected as in table II.

Drug	Route	Dose	Number of Subjects	Effect on Cardiac Sphincter
$PGF_{2\alpha}$	Intravenous bolus	0, 2·5, 5·0, 10·0, 40·0 ($\mu g\ kg^{-1}$)	7	None
$PGF_{2\alpha}$	Intravenous infusion for 20 min	0·05 ($\mu g\ kg^{-1}\ min^{-1}$)	3	Contraction
		0·1	2	Contraction
		0·2	3	Contraction
		0·4	3	Contraction
		0·8	4	Contraction
PGE_2	Intravenous infusion for 20 min	0·01 ($\mu g\ kg^{-1}\ min^{-1}$)	2	None
		0·02	2	None
		0·04	2	None
		0·08	3	None
PGE_2	Intravenous infusion for 20 min	0·08 ($\mu g\ kg^{-1}\ min^{-1}$)	3	Inhibition of contractions to pentagastrin
Pentagastrin	and intravenous bolus over 15 sec every 10 min	0·1 or 0·2 ($\mu g\ kg^{-1}$)		
Indomethacin	per rectum	200 mg	7	Contraction

Table IV *Summary of studies*

convincing inhibition was observed, but the sphincteric contractions due to the pentagastrin increased after cessation of the PGE_2 infusion (fig 3, table IV).

INTRARECTAL INDOMETHACIN

Intrarectal indomethacin (2 × 100 mg suppositories) was administered to seven subjects following the 20-min basal period and resulted in a slow rise in cardiac sphincter pressure above the basal level, which was apparent during the 90 min following the drug ($P < 0·001$, fig 4, table IV). Glycerine suppositories had no effect on cardiac sphincter pressure.

The results of the various studies are summarized in table IV.

Discussion

The results of this study show that circulating exogenous $PGF_{2\alpha}$ produces marked and sustained contractions of the lower oesophageal sphincter. This action is dose-dependent, some response being recorded even at the lowest level of 0·05 $\mu g\ kg^{-1}\ min^{-1}$. The dose-response curve suggests that maximal response to $PGF_{2\alpha}$ was not reached, but it was thought unwise to exceed the level of 0·8 $\mu g\ kg^{-1}\ min^{-1}$, because of possible occurrence of unwanted effects. Even at the dose range of $PGF_{2\alpha}$ used in this study increases in sphincteric pressures were comparable in magnitude to those reported by Cohen and Lipshutz (1971) during

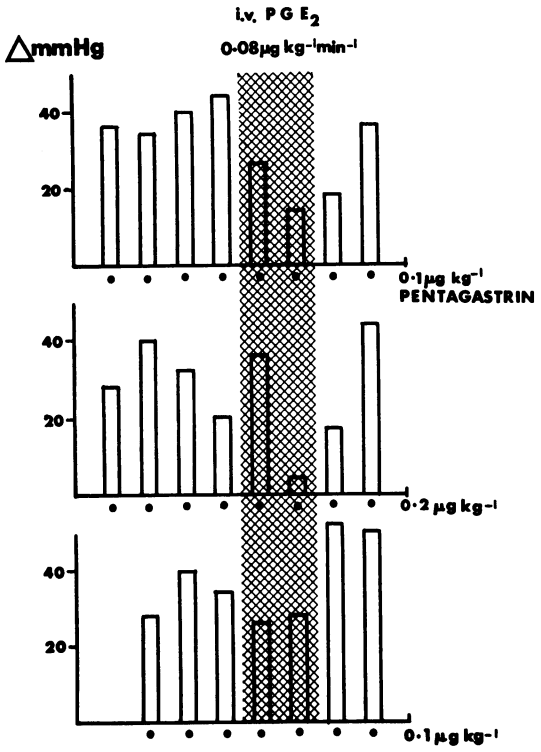

Fig 3 *Effect of intravenous infusion of PGE_2 0·08 μg kg^{-1} min^{-1} on cardiac sphincter contractions in response to serial bolus injections of pentagastrin in three subjects.*

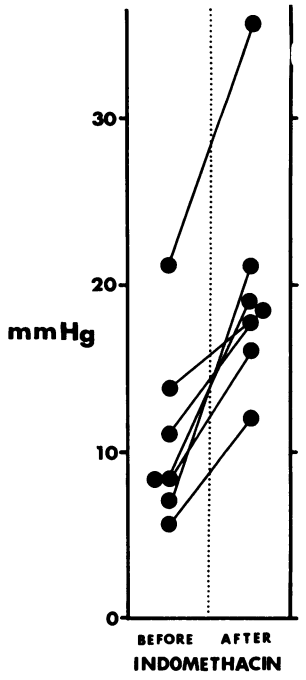

Fig 4 *Response of the cardiac sphincter in seven subjects to intrarectal indomethacin 200 mg. Left column = mean basal pressure, right column = highest pressure during any five min period after the drug.*

maximal stimulation of the lower oesophageal sphincter by exogenous gastrin. The contractions of the sphincter do not appear to have been caused by the release of gastrin, because levels of circulating immunoreactive gastrin were unaffected by the prostaglandin. The reasons for the delayed onset of sphincter contraction during the infusion of $PGF_{2\alpha}$ and the persistence of elevated sphincter pressures after infusion of the PG was stopped are conjectural, but may have been due to a build up of active metabolites. Other reasons could be saturation of the 15-dehydroxylase enzyme system, release of secondary active agents, or saturation of the plasma-binding sites for prostaglandin $F_{2\alpha}$.

Although PGE_2 at dose levels which are equally potent in obstetrics had no effect on resting cardiac sphincter pressures, the inhibitory action of this PG on the sphincter was demonstrated in two indirect ways. First, contractions of the sphincter to serial bolus injections of pentagastrin were diminished by prostaglandin E_2. Secondly, the administration of indomethacin, which is a potent inhibitor of prostaglandin synthetase (Aiken and Vane, 1971; Ferreira, Moncada, and Vane, 1971; Vane, 1971), was followed by increased cardiac sphincter pressures. Blood levels of indomethacin reach a peak approximately one hr after rectal administration (Holt and Hawkins, 1965), which coincides approximately with the observed effect on the cardiac sphincter. The inhibitory effects of PGE_2 on the human cardiac sphincter agree well with observations made by Goyal and Rattan (1973) in the oppossum, although the doses used by these workers were higher (0·15 to 8 μg kg^{-1}). Pharmacological analysis by those authors suggests that PGE_2 acted directly on the smooth muscle cells (Goyal and Rattan, 1973).

Neither prostaglandin used in this study had any effect on the contractions of the gastric fundus and although the amplitude of oesophageal peristaltic waves was consistently increased after $PGF_{2\alpha}$, the increase was not significant at the highest dose. This may mean that these tissues are unresponsive to PGs, or that their sensitivity to these compounds is lower. Sensitivity to exogenous PGs may differ in various regions of the human alimentary tract. For example, $PGF_{2\alpha}$ at dose levels used in the present study has been shown to inhibit segmental contrac-

tions in the jejunum and ileum, but not in the sigmoid colon (Cummings, Newman, Misiewicz, Milton-Thompson, and Billings, 1973; Hunt, Dilawari, and Misiewicz, 1975). The negative results in these areas may, however, be also due to the inability of the recording system to detect changes. In the gastric fundus muscle contractions need not necessarily be accompanied by alterations of intraluminal pressure, whilst tubes perfused at slow rates may underestimate the amplitude of oesophageal peristaltic contractions (Hollis, Levine, and Castell, 1972).

The present observations may have certain interesting physiological and therapeutic implications. Although many biogenic agents have been shown to affect the pressure in the lower oesophageal sphincter, their relative physiological importance is still uncertain. Thus the sphincteric pressure can be increased by cholinergic and decreased by anticholinergic stimuli (Bettarello, Tuttle, and Grossman, 1960; Roling, Farrell, and Castell, 1972). Adrenergic neurotransmitters also affect the tone of the oesophageal sphincter, α-adrenergic activity producing contractions and β-adrenergic receptors mediating relaxations (Christensen, 1970; Christensen and Dons, 1968; Christensen and Daniel, 1968; Misiewicz, Waller, Anthony, and Gummer, 1969). Other results suggest that, at least in the opossum, basal sphincteric pressure may depend on α-adrenergic activity. On the other hand the rapid relaxation to swallowing may not be mediated through the β-adrenergic pathway, but via non-adrenergic inhibitory nerves (Tuch and Cohen, 1973; Dimarino and Cohen, 1973). Another group of agents that change the pressure in the lower oesophageal sphincter are the alimentary polypeptide hormones. Gastrin or pentagastrin raises the sphincter pressure and the effects can be antagonized by secretin (Giles, Mason, Humphries, and Clark, 1969; Castell and Harris, 1970; Cohen and Lipshutz, 1971; Isenberg, Csendes, and Walsh, 1971; Lipshutz, Hughes, and Cohen, 1972). It has been suggested that gastrin plays a major role in the control of sphincter tone, but others feel that the effects on the cardiac sphincter are pharmacological rather than physiological (Grossman, 1973). There is impressive evidence for the physiological role of gastrin in relation to the oesophageal sphincter in the opossum (Lipshutz *et al*, 1972), but in man peak sphincteric pressure responses and peak gastrin levels after meals do not coincide in time (Morris, Schoen, Brooks, and Cohen, 1974).

Results of this study, together with the data of Goyal and Rattan (1973), indicate that PGs should now be included in the array of biogenic agents that affect the activity of the cardiac sphincter.

Experimental evidence strongly suggests that the tone of alimentary muscle in some experimental animals is maintained by intramural generation of PGE_2 (Ferreira, Herman, and Vane, 1972; Eckenfels and Vane, 1972; Davison, Ramwell, and Willis, 1973). Prostaglandins of the E and F group are released from animal gut tissue in response to mechanical, hormonal, chemical, and nervous stimuli (Bennett, Friedmann, and Vane, 1967; Coceani, Pace-Asciak, Volta, and Wolfe, 1967; Ramwell and Shaw, 1968; Collier, 1974). Predominantly E type PGs are released from frog oesophageal tissue strips, the amount being greatly increased by electrical stimulation (Rashid, 1971). Prostaglandin E_2 is also released by the rat oesophagus in response to mechanical compression (Collier, 1974). Human gastric mucosa contains PGE_2 (Bennett *et al*, 1973) which is liberated in response to mechanical stimulation (Bennett, Gradigde, and Stamford, unpublished). It should be mentioned, however, that so far there have been no studies of the occurrence of PGs in the human oesophagus. Our results with infused PGE_2 show it to have an inhibitory effect on the cardiac sphincter, whilst the increased sphincteric pressure we observed after intrarectal indomethacin suggests that PGE_2 may be produced endogenously in active amounts in the human gullet.

The role that PGs may have in regulating the tone of the lower oesophageal sphincter, the mechanism of relaxation during swallowing, and the way PGs may interact with other pharmacological agents must be defined by further studies in animals and man.

The effects of PGE_2 are also of interest in relation to pathological conditions and the action of drugs on the oesophagus. Tissue synthesis of PGs increases in inflammation. Increased amounts of PGE_2 released in the presence of oesophagitis might therefore lower sphincter tone, with deleterious effects on the competence of the gastrooesophageal junction. It is also of interest that local release of PGs due to inflammation may determine the onset of symptoms in patients suffering from reflux. This is because Ferreira (1972) has shown that PGs lower the pain threshold to other locally released products of inflammation, such as histamine or bradykinin. Specific PG-synthetase inhibitors may therefore become useful in the treatment of both the cause and the symptoms of gastrooesophageal reflux, although the inhibitors available at present are obviously unsuitable for this purpose.

The relevance of the contractile response of the cardiac sphincter to $PGF_{2\alpha}$ lies mainly in the therapeutic area, because so far this PG has not been isolated from the human upper alimentary tract.

Analogues of $PGF_{2\alpha}$, active on the sphincter when given by mouth, but free of unwanted effects, could be beneficial in the treatment of gastro-oesophageal reflux. This is particularly so because sphincteric relaxation to swallowing was not impaired even at the height of the response to this PG, whilst the increase in the sphincteric tone was prolonged. Higher doses or analogues of $PGF_{2\alpha}$ may significantly increase the amplitudes of oesophageal peristaltic contractions, making clearance of acid from the gullet more efficient. The profound inhibition of gastric acid secretion by oral methyl derivatives of PGE_2 shows that potent pharmacological effects are possible in a related field (Karim, Carter, Bhana, and Ganesan, 1973a, b; Fung, Karim, and Tye, 1974).

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