0.2 mg/kg, days 30 and 37), local radiotherapy (500 rads, days 30 and 37), and flurbiprofen, day 25 onwards. The tumours were excized after 6 weeks.

The extracts of tumours from mice given flurbiprofen contained 60 ± 16 to 74 ± 30 ng PGE_2 equivalents/g wet tumour, compared with 125 ± 19 ng/g in controls (all $P < 0.02$). Tumour weights were similar to controls (0.99 ± 0.19 g) except in mice receiving flurbiprofen with radiotherapy (0.45 ± 0.05 g) or radiotherapy + chemotherapy (0.29 ± 0.05 g) ($P < 0.02$ and < 0.01 respectively).

We conclude that flurbiprofen reduced the growth of the primary tumours and their ability to synthesize PGs, tended to increase survival time following removal of the primary tumour, and increased the effect of radiotherapy and chemotherapy.

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C.21

The effects of prostaglandin D_2 on the circular muscle of guinea-pig isolated ileum and colon

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Prostaglandin (PG)D can be formed by gastrointestinal tissue (Nugteren & Hazelhof, 1973). PGD_2 contracts the gut longitudinal muscle of various species (e.g. Hamberg, Hedqvist, Strandberg, Svensson & Samuelsson, 1975). Apart from rabbit stomach (Moncada, Mugridge & Whittle, 1977) the effects of PGD_2 on gastrointestinal circular muscle have not been studied. We report experiments on circular muscle of guinea-pig ileum and colon. Spiral strips approximately 3 mm wide and 30 mm long were cut from the distal ileum and distal colon of male guinea-pigs weighing approximately 400 g. Each strip was suspended under a load of 1 g in Krebs solution at 37°C bubbled with 5% CO_2 in O_2. Isotonic responses were measured using transducers and pen recorders.

The circular muscle strips of guinea-pig ileum had no tone, and since PGD_2 did not cause a contraction we looked for an inhibitory effect on submaximal responses elicited with 1.5 mg/ml KCl.

PGD_2, PGE_2 or $PGF_{2\alpha}$ (1 μg/ml) given 1 min before the KCl reduced the contraction to KCl by 21 ± 6, 90 ± 3 and 5 ± 2% (mean ± s.e. mean; $n = 8$, 7 and 7 respectively); PGD_2 2 μg/ml reduced the response to KCl by 37 ± 4% ($n = 7$). The findings with PGE_2 and $PGF_{2\alpha}$ confirm those of Bennett, Eley & Scholes (1968) and Bennett, Eley & Stockley (1975).

In colonic circular muscle PGD_2, by contrast, caused contraction, 70 ± 10 ng/ml being required for a threshold contraction ($n = 9$). As found by Fleshler & Bennett (1969), $PGF_{2\alpha}$ contracted this tissue (threshold concentration; 8 ± 2 ng/ml, $n = 9$) and PGE_2 caused relaxation. We confirmed that the PG antagonist SC-19220 blocks the contractions to $PGF_{2\alpha}$ but not the relaxations to PGE_2 (Bennett & Posner, 1971). SC-19220 (80–130 ng/ml) also prevented the contraction to PGD_2 (1 μg/ml), but it greatly reduced muscle tone and hampered detection of relaxation. However, PGD_2 (1 μg/ml) now reduced submaximal contractions to acetylcholine by 29 ± 10% ($n = 4$) whereas in the presence of $PGF_{2\alpha}$ (1 μg/ml) the acetylcholine-induced contractions were virtually unchanged (101 ± 3% of controls, $n = 4$).

Thus, in colonic circular muscle, PGD_2 exerted a predominant excitatory '$PGF_{2\alpha}$-like' activity which overshadowed the inhibitory 'PGE_2-like' response. However, in the ileum circular muscle only a 'PGE_2-like' response occurred with PGD_2, and this tissue is virtually unresponsive to $PGF_{2\alpha}$.

We suggest that there are regional differences in the distribution of receptors activated by PGD, E and F_α compounds, that the 9-hydroxyl group is important for activation of receptors stimulated by $PGF_{2\alpha}$, and that a 9- or 11-oxo group is important for activation of receptors stimulated by PGE_2.

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C.22

A study of receptors activated by analogues of prostaglandin H_2

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The prostaglandin (PG) endoperoxides PGG_2 and PGH_2 are biologically active intermediates in the formation of PGs and thromboxanes. It is not known whether the endoperoxides and PGs act on the same receptors. We have studied this problem using the PG antagonist SC-19220 (Sanner, 1969).

Rat gastric fundus strips and segments of guinea-pig ileum were suspended under loads of 0.5–1.0 g in Krebs solution at 37°C bubbled with 5% CO_2 in O_2. Isotonic contractions of longitudinal muscle were registered with transducers and pen recorders.

PGE_2 and the PGH_2 analogues, (15S)-hydroxy-9α,11α- and (15S)-hydroxy-11α,9α-(epoxymethano)-prosta-5Z,13E-dienoic acids (U-44069 and U-46619) contracted both tissues. This was shown by cumulative dose-response curves in the rat stomach and by responses to single doses in the guinea-pig ileum.

On the rat stomach the potencies were PGE_2 > U-46619 > U-44069, and the maximum contractions were usually similar. SC-19220 (5 μg/ml) shifted the dose response curve of PGE_2 to the right (Table 1). In contrast, there was no significant effect on the dose-response curves of the analogues ($P > 0.2$). The responses of guinea-pig ileum to the analogues were small and variable. The maximum responses to U-44069 and U-46619 were, respectively, 11 ± 27 (±s.e. mean) and 26 ± 16% of that to PGE_2. Approximate doses required to produce ED_{50} responses were 4 μg/ml for the analogues and 10 ng/ml for PGE_2. SC-19220 2 μg/ml reduced responses to PGE_2 more than those of the analogues. Responses to doses of PGE_2, U-44069 and U-46619 that produced approximately 50% of maximum contractions were reduced by 73 ± 3, 54 ± 6 and 35 ± 9% respectively.

Table 1 ED_{50} concentrations (ng/ml) before (control) and after addition of SC-19220, 5 μg/ml

Drug	*Control*	n	+SC-19220	n
PGE_2	2.7 ± 0.1	23	7.0 ± 1.3*	8
U-44069	15.7 ± 1.6	13	10.6 ± 2.5	5
U-46619	10.5 ± 1.8	13	14.0 ± 4.3	7

Mean ± 1 s.e. mean.
* $P < 0.001$.

We conclude that the potencies of the analogues relative to PGE_2 vary with the tissue, and that at least so far as the rat stomach is concerned, the receptors for PGE_2 and the analogues are different.

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