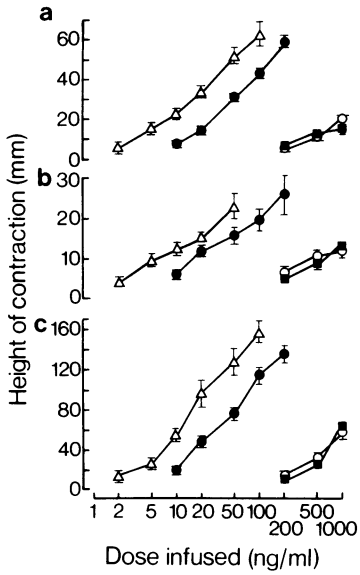

Figure 1 Comparative bioassay of prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) (△) and its pulmonary metabolites 13,14-dihydro-PGF (●), 15-keto-$PGF_{2\alpha}$ (○) and 13,14-dihydro-15-keto-$PGF_{2\alpha}$ (■) on (a) rat stomach strip, (b) chick rectum and (c) rat colon. Prostaglandin $F_{2\alpha}$ or metabolites were given as random 2 min infusions into the Krebs solution superfusing the assay tissues. The height of contraction of the assay tissues was plotted against the log dose of agonist. Each point is the mean of 9–11 experiments. Vertical bars show s.e. mean.

PGE_1 and dihydro-PGE_2 did not give parallel bioassay. Similar results were obtained with PGE_2 and 13,14-dihydro-$PGF_{2\alpha}$. However, the differences obtained would not be sufficient to allow distinction between these PGs and metabolites in a biological fluid. 13,14-dihydro-$PGF_{2\alpha}$ was approximately 1.7 times as active as $PGF_{2\alpha}$ and approximately 3.0 times as active as PGE_2 on the oestrous rat uterus.

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Prostaglandins and tone in isolated strips of mammalian bladder

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It has been demonstrated in a group of patients with paralysed atonic bladders that the intravesical instillation of prostaglandin E_2 (PGE_2) restores a normal pattern of micturition (Bultitude, 1973). The local production of prostaglandins has been implicated in the maintenance of tone and spontaneous activity of smooth muscle of the intestine (Ferreira, Herman & Vane, 1972), uterus (Vane & Williams, 1973) and trachea (Farmer, Farrar & Wilson, 1974). The object of the present investigation was to determine whether prostaglandins have a similar function in the bladder.

Strips of either detrusor or trigone muscle from the bladder of rabbit, rat, cat, dog, sheep, guinea-pig or human were suspended in Tyrode's solution at 37°C, bubbled with O_2 (95%):CO_2 (5%) mixture. A tension of 1 g was applied. Contractions were measured isometrically and displayed on a Servoscribe 1 s potentiometric recorder.

Prostaglandin E_2 (0.2–6.0 μg/ml) and prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) (0.2–6.0 μg/ml) caused contractions of the strips, but the log dose-response curve obtained was much less steep than that of carbachol. The tone and spontaneous activity of the strips was reduced by indomethacin (0.5–2 μg/ml), meclofenamic acid

(0.5–1 μg/ml) and flufenamic acid (5–10 μg/ml) in all species except the guinea-pig. The addition of PGE_2 and $PGF_{2\alpha}$ (10–20 ng/ml) reversed the effects of these substances causing a return of tone and spontaneous activity. Bioassay of the bath fluid of the rabbit detrusor strips and thin layer chromatography done in association with N.G. Bowery, indicated, by the R_f value of the biological activity, the presence of PG-like activity of the E-series. In the presence of indomethacin no activity was detectable.

The addition of physostigmine (1 μg/ml) to the rabbit isolated detrusor strip produced an increase in tone and spontaneous activity which was prevented by the prior addition of indomethacin. Prostaglandin E_2 reversed this effect of indomethacin. Hyoscine (300 ng/ml), which did not affect the resting tone or spontaneous activity, abolished the response to physostigmine. These results suggest that there may be a link between acetylcholine output and PG production in the bladder preparation. Preliminary experiments with hemicholinium-3 support this possibility.

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Effects of metyrapone on rat uterine prostaglandin release and on spontaneous smooth muscle activity *in vitro*

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Parnham & Sneddon (1975) have shown that metyrapone, an inhibitor of corticosteroid biosynthesis (Chart & Sheppard, 1959), when administered *in vivo* inhibits the subsequent release of prostaglandin F (PGF) from the isolated pregnant rat uterus. It also inhibits the conversion of ^{14}C-arachidonic acid to prostaglandin E_2 (PGE_2) by crude homogenates of pregnant rat uteri at the same time stimulating the synthesis of labelled prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$). In an attempt to clarify the action of metyrapone its direct effect on the isolated pregnant rat uterus has been investigated.

Uteri were removed from pregnant rats on the morning of day twenty-two. Individual horns were mounted in 75 ml organ baths and bath fluid collected every 15 min for 1 h, as described previously (Vane & Williams, 1973), while uterine activity was recorded isotonically. Metyrapone (to give 0.5, 1, 2 or 4 mM) was injected into one bath at the start of the experiment and the corresponding volume of vehicle (0.33M (+)-tartaric acid; 0.05–0.4 ml) was injected into a second organ bath containing the contralateral uterine horn. Both solutions were left in contact with the tissue for 15 min, and then washed out. Prostaglandins were extracted from bath fluid as described by Vane & Williams (1973), subjected to column chromatography to separate PGs E and F (Parnham & Sneddon, 1975) and the relevant fractions were resuspended in 2 ml saline for bioassay either on the isolated rat colon against authentic $PGF_{2\alpha}$ or on the isolated rat stomach strip against authentic PGE_2. At low doses of metyrapone the release of both PGE and PGF was stimulated when compared with controls ($291 \pm 67\%$ and $182 \pm 25\%$ at 0.5 mM, respectively; 4 exp/dose); but at higher doses PGF release was inhibited ($65 \pm 8\%$ at 4 mM), whereas PGE release was unaffected.

Metyrapone rapidly inhibited spontaneous uterine contractions which reappeared within 5–10 min following washout. This inhibition was dose-dependent and involved reduction of tone at high doses. Similar dose-dependent inhibition of spontaneous contractions by metyrapone, was observed on the isolated rabbit ileum. This did not involve a reduction in tone at the doses used. Propranolol (1 μg/ml) antagonized the inhibitory effect of isoprenaline on this preparation, but had no effect on the response to metyrapone. The dose-response curve to metyrapone on the rabbit ileum was similar to that for papaverine, which was