important changes in uterine PG production at term and that such synthesis is involved in parturition (Aiken, 1972).

The preparation of pregnant uteri, extraction and bioassay of PG's were carried out as described previously (Vane & Williams, 1972). Spontaneous contractions in uteri 17–20 days pregnant were abolished by indomethacin (2·8–5·6 $\mu$M) but higher doses of indomethacin (5·6–11·2 $\mu$M) were required to suppress spontaneous contractions of uteri from rats 21–22 days pregnant. After indomethacin, activity similar in frequency and form to that seen in untreated preparations could be restored by addition of $PGE_2$ or $PGE_{2\alpha}$ (4–16 ng/ml) to the bathing fluid.

Release of PG-like activity into the bathing fluid was also measured. Uteri taken at 19–21 days of pregnancy released 66–156 (ng/g)/h of F type PG, those taken on day 22 released 250–680 (ng/g)/h. Thus, there was an increase at term in the capacity of the tissue to synthesize PG's.

PG synthesis by uterine homogenates from pregnant rats was also studied. After removal of the foetuses, uteri were washed in ice-cold Krebs solution, dried and weighed. Endometrial and myometrial fractions were prepared by scraping the uterus and their separation ascertained histologically. The fractions were homogenized in ice-cold phosphate buffer (ph 7·4) and centrifuged (2,500 g min). Aliquots (0·5–1 ml) of the supernatant were added to 1–1·15 ml of incubation mixture (sodium arachidonate 15 $\mu$M; reduced glutathione 325 $\mu$M and hydroquinone 91 $\mu$M in phosphate buffer). Samples were incubated aerobically with or without indomethacin (5·6-44·8 $\mu$M) for 60 min at 37° C. The reaction was stopped by heating in boiling water for one minute. After extraction, the PG content was estimated in terms of $PGF_{2\alpha}$ by parallel bioassay. Net PG production by the endometrial fraction on days 19–21 was $1,790 \pm 349$ ng/g wet weight of tissue (mean, S.E. of mean, $n=9$); synthesis increased sharply to $24,220 \pm 5,743$ ng/g ($n=9$) on day 22. Net PG synthesis by the myometrial fraction was much lower ($414 \pm 129$ ng/g; $n=3$; on days 19–21) indicating that the endometrium is the major source of uterine PG's.

The establishment of a relationship between PG synthesis and uterine contractions *in vitro* and the dramatic increase in endometrial PG synthesis at term suggests that local prostaglandin production has an important role in parturition.

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## Further experiments to establish that the analgesic action of aspirin-like drugs depends on the inhibition of prostaglandin biosynthesis

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Acidic anti-inflammatory drugs inhibit prostaglandin biosynthesis (Vane, 1971; Ferreira, Moncada & Vane, 1971; Smith & Willis, 1971). Ferreira (1972) suggested that prostaglandins only have a facilitatory role in inflammatory pain, for low concentrations cause a long-lasting sensitization to mechanical or chemical stimulation. Only in much higher concentrations than appear in inflammation do they induce overt pain.

The nociceptive activity of bradykinin in dog spleen is blocked by a peripheral action of aspirin-like drugs (Lim, Guzman, Rodgers, Goto, Braun, Dickerson & Engle, 1964). We have, therefore, investigated the interactions between bradykinin, prostaglandins and aspirin-like drugs in dog spleen.

Dogs were anaesthetized with pentobarbitone sodium (20 mg/kg I.V.). A small branch of the splenic artery was cannulated retrogradely with polyethylene tubing for intra-arterial injections; the splenic vein was also cannulated for removal of blood. Splenic venous blood was withdrawn at 10 ml/min to superfuse a series of isolated assay tissues to detect prostaglandins (a rat stomach strip, chick rectum and rat colon) and bradykinin (a cat terminal ileum) by the blood-bathed organ technique (Vane, 1964; 1969). After superfusing the assay tissues the blood was returned to the animal intravenously.

Intra-arterial injections of bradykinin (5–20 $\mu$g) released prostaglandin-like activity into the splenic venous blood, in amounts (in terms of $E_2$) varying from 1–5 ng/ml. The release was blocked by indomethacin (2–5 mg/kg intravenously).

Other dogs were lightly anaesthetized with thiopentone (30 mg/kg) and chloralose (30–50 mg/kg) intravenously. Bradykinin (0·1–2 $\mu$g) intra-arterially into the spleen produced increases in arterial blood pressure proportional to the dose. This reflex pressor effect of bradykinin is due to stimulation of sensory nerves and is an index of the nociceptive activity of bradykinin (Hashimoto, Kumakura & Taira, 1964). Prostaglandin $E_1$ or $E_2$ (5–20 $\mu$g) injected together with bradykinin potentiated the reflex pressor response although prostaglandins by themselves were vasodepressor. Indomethacin (1–8 mg/kg) reduced the effect of intra-splenic bradykinin so that four times the dose had to be used to induce the same pressor effect. After indomethacin, prostaglandin $E_1$ or $E_2$ given as intra-splenic injections (5–20 $\mu$g) or slow infusions (50 ng/min) increased once more the sensitivity to bradykinin.

These results add force to the theory that the analgesic action of aspirin-like drugs is peripheral and is due to inhibition of prostaglandin formation. The prostaglandin released within the spleen sensitizes sensory nerve endings to the nociceptive action of bradykinin. This facilitation may also apply to other chemical or mechanical stimuli. The action of aspirin would then be due to the removal of the prostaglandin-induced facilitation, which accounts for the fact that aspirin is only a weak analgesic.

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## The actions of prostaglandins $A_1$ and $A_2$ on airway resistance and compliance in the cat

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Main (1964) showed that prostaglandin $E_1$ ($PGE_1$) increased the 'resistance to inflation' of cat lungs studied by the method of Konzett & Rössler. This could be interpreted as either an increase in airway resistance or a decrease in compliance. Rosenthale, Dervinis