Prostaglandins: a report on early clinical studies

J. W. Hinman
Ph.D.

Head, Natural Products Research,
The Upjohn Company, Kalamazoo, Michigan

Summary
The prostaglandins are a unique group of pharmacologically active lipids which are widely distributed in mammalian tissues and body fluids. The chemistry of this family of compounds has been established in elegant detail. Research quantities of these highly active natural compounds were obtained by enzymatic bioconversion of essential fatty acids and now studies devoted to the elucidation of their physiological roles and their clinical potential are progressing rapidly. Fields of greatest current interest in clinical medicine include renal-cardiovascular research, induction of labour and therapeutic abortion, control of the reproductive cycle (including fertility control), bronchodilation, enhancement of nasal patency and antisecretory activity. Results available to date are too preliminary for many conclusions to be drawn, but are sufficiently encouraging to assure continued and expanding efforts in several fields.

Introduction
Observations made in the early 1930s indicated the presence of a pharmacologically active principle in human seminal fluid. Euler (1936) showed that a lipid-soluble acid with the same biological characteristics could be extracted from sheep vesicular glands and could be differentiated from other biologically active substances known at the time. He named the principle ‘prostaglandin’. Bergström & Sjövall (1960) succeeded in isolating two active crystalline compounds from extracts of sheep seminal vesicles and these were designated prostaglandins E and F. Within a very short time Bergström and his co-workers, particularly Samuelsson and Sjövall isolated and characterized a whole family of prostaglandins (Bergström, 1967). Six of these are regarded as primary prostaglandins and designated as PGE₁, PGE₂, PGE₃, PGF₁α, PGF₂α, and PGF₃α. The rest of the naturally occurring members of the family are derived metabolically from these six. All are related chemically to the hypothetical parent fatty acid prostanoic acid (Fig. 1). All of the naturally occurring prostaglandins (PGs) are unsaturated hydroxy-acids containing a 5-membered ring in a 20-carbon skeleton. For the purposes of this survey, the most important compounds of this series are PGE₁, PGE₂, PGF₁α and PGF₂α (Fig. 1).

Once the chemical structure of the prostaglandins was established, it became apparent that a formal relationship existed between them and certain unsaturated fatty acids which nutritionists have long referred to as the essential fatty acids. These compounds were found to serve as precursors for the biosynthesis of prostaglandins (van Dorp et al., 1964; Bergström et al., 1964; Wallach, 1965). Thus the in vitro production of prostaglandins by the enzymatic bioconversion utilizing these unsaturated fatty acids and enzyme systems derived from animal seminal vesicles provided for the first time adequate amounts of these rare compounds to permit widespread biological evaluation (Hinman, 1967; Ramwell et al., 1968). A great deal of effort has been devoted to the total chemical synthesis of prostaglandins (Pike, 1970) and for the future this will most likely be the preferred method of production.

Occurrence and biological activities
Prostaglandins occur in the highest concentrations in human and sheep seminal fluid, but they also are present at low concentrations in a wide variety of tissues and body fluids including kidney, lung, nervous tissue, menstrual fluid, thymus, spleen, uterus, amniotic fluid at term, and adipose tissue. With the exception of human seminal fluid and in rare pathological situations, e.g., human medullary carcinoma of the thyroid (Sandler et al., 1968), prostaglandins have been found in very low concentrations of a few nanograms to a few micrograms per gram of wet tissue. Positive identification and quantitation of a specific prostaglandin in biological samples is still difficult and time-consuming, and many results which have been reported should be
confirmed when improved methods become available. Nevertheless there is no doubt that prostaglandins are widely distributed in mammalian tissues and they have significant—though incompletely understood—physiological activities.

The activities originally ascribed to the prostaglandins were stimulation of smooth muscle and vasodepression. Many diverse biological activities are known now and they vary considerably depending on the structure of the individual compound. Prostaglandin E₁ or PGE₁, the most thoroughly studied member in the family, exhibits potent action as a non-vascular smooth muscle stimulant, a vasodepressor agent, a nasal vasconstrictor, and as an inhibitor of lipolysis, gastric secretion and platelet aggregation. PGE₁ causes sedation when administered into brain ventricles and causes persistent miosis and a rise in intraocular pressure when injected into the anterior chamber of the eye. It exerts synergistic and antagonistic actions with catecholamines in some organs. The PGAs exhibit many of the activities of the PGEs in that they have a qualitatively similar action on blood pressure and gastric secretion but lack the potent action on non-vascular smooth muscle. The PGFs tend to be pressor rather than depressor and cause venoconstriction in some cases. In most of their areas of activity the prostaglandins are among the most potent compounds known with activities in some systems at concentrations of 0.01 ng/ml in vitro and at 10 ng/kg in vivo. Nerve activity is known to stimulate prostaglandin formation and release both centrally and peripherally. Prostaglandins have been implicated in anaphylaxis, inflammation and in parturition. Several excellent reviews are available on the biological actions of the prostaglandins (Bergström et al., 1968; Pickles, 1969; Horton, 1969).

**Metabolism**

It was apparent from the early studies with isotopically labelled prostaglandins that these compounds are rapidly metabolized when introduced
into the circulation of an intact animal. Largely through the work of Ånggård, Samuelsson and Hamberg many of the metabolites have been thoroughly characterized and some of the enzyme systems responsible for the degradative reactions have been studied. Relatively large amounts of certain metabolites occur in human seminal fluid along with the primary prostaglandins. These are PGA₁, PGA₂, PGB₁ and PGB₂, which are produced by dehydration and isomerization (Fig. 1) from the primary E compounds, and the four corresponding 19-hydroxy compounds formed by enzymatic hydroxylation of the PGAs and PGBs (Hamberg & Samuelsson, 1967).

In the lungs the PGEs are metabolized by reduction of the Δ¹⁵ double bond and by oxidation of the secondary hydroxyl group at carbon atom 15 to a carbonyl group (Ånggård & Samuelsson, 1966). Reduction of the double bond did not appreciably alter the biological activity of the PGE₁, but oxidation of the 15-hydroxyl to a ketone caused drastic reduction of activity in two systems studied. In vitro incubation studies by Hamberg (1968) showed that the prostaglandins are subject to β-oxidation in rat liver mitochondria. Evidence of β-oxidation has also been reported in the intestine (Parkinson & Schneider, 1969). These studies revealed that the prostaglandins undergo one or two steps of β-oxidation of the carbonyl side chain to yield dinor and tetranor metabolites. β-Oxidation from the methyl end has been demonstrated also after an initial ω-hydroxylation yielding urinary metabolites which are dicarboxylic acids. The major urinary metabolites of the PGEs and PGFs in man have carbonyl side chains with 2 or 4 carbons removed, the Δ¹⁵ double bond reduced and the 15-hydroxy group oxidized to a ketone (Hamberg & Samuelsson, 1969; Granström & Samuelsson, 1969). Recent experiments have shown that dinor and tetranor PGE₁ and PGF₁α are poor substrates for prostaglandin dehydrogenase (Nakano, Anggard & Samuelsson, 1969). These findings suggest that catabolism of the PGs is probably initiated by the dehydrogenase and reductase reactions. It is worthy of note that of the prostaglandins which have been studied clinically only PGA₁ and PGA₂ escape rapid inactivation in the pulmonary circulation (McGiff et al., 1969) and are, therefore, the only ones which might function as circulating hormones.

Clinical studies

The first human pharmacology studies with a purified prostaglandin were reported by Bergström et al. (1959). Chemically pure PGE₁, isolated from sheep vesicular glands, was infused in doses of 0·2–0·7 µg/kg/min in two healthy male subjects over periods of 4–10 min. ‘Tachycardia, reddening of the face, headache and an oppressive feeling in the chest were noted.’ It was noted also that blood pressure fell moderately. During the 1950s and early 1960s some attempts were made to relate the occurrence of prostaglandins in seminal fluid to some function or role in reproduction, but no definitive studies were possible until practical research quantities of the pure compounds became available and appropriate animal studies could be carried out. This was accomplished during the mid and late 1960s. During this period the clinical, cardiovascular and metabolic responses of infusions of PGE₁ to healthy volunteers were reported (Bergström et al., 1965; Carlson, Ekulund & Örög, 1968; 1969). These studies demonstrated clearly the potential of PGE₁ to induce profound pharmacological responses in man and they established the safety of certain dosage regimes, but they did not point directly to clear-cut clinical utility. However, other studies both in animals and man revealed areas of clinical investigation which may have practical application. The main purpose of this survey is to highlight these developments.

Renal-cardiovascular pharmacology

PGE₁ and PGE₂ are powerful vasodilators causing a fall in blood pressure, increased cardiac output and increased heart rate. The decrease in blood pressure appears to be a direct vasodilator effect on resistance vessels which is not blocked by α- and β-adrenergic blocking agents or prior administration of atropine, lysergic acid diethylamide or the antihistamine, tripelennamine (Strong & Bohr, 1967). The cardiovascular effects of PGF₂α are complicated by variations of response in different species. Although less potent, like the PGEs, it is depressor in the cat and rabbit while in the rat and dog, unlike the PGEs, it is pressor. In the dog i.v. injections of PGF₂α cause a rise in blood pressure that is associated with an increase in both cardiac output and peripheral resistance brought about by vasoconstriction and increased venous return (DuCharme et al., 1968). In common with the PGE compounds, the PGFs possess potent smooth muscle-stimulating activity. The cardiovascular effects of PGF₂α in man are strikingly different from those of PGE₁ and are quantitatively different from the effects of PGF₂α in the dog. Continuous infusion of 0·01–2·0 µg/kg/min of PGF₂α for 60 min in six volunteers produced no effect on blood pressure, heart rate, ECG or respiration rate and none of the volunteers complained of any discomfort during or after the infusion (Karim et al., 1969a). One of the same subjects was infused with 0·2 µg/kg/min of PGE₁ for 30 min and this produced the same objective and subjective responses reported earlier by Bergström et al. (1959, 1965).
The most interesting of the prostaglandins with respect to renal and cardiovascular activities are the PGA compounds. PGA₁ was first isolated and characterized as one of the PGs present in the mixtures obtained from the in vitro enzymatic bioconversion of bis-homo-γ-linolenic acid utilizing the sheep seminal vesicle system (Daniels et al., 1965). This compound was detected and distinguished from the other prostaglandins because of its striking vasodepressor activity and lack of non-vascular smooth muscle-stimulating activity. Similar activity had been detected in the mixtures of lipids extracted from renal medulla (Muirhead et al., 1965). Lee et al., (1965) isolated a lipid acid with similar properties from rabbit renal medulla and named it medullin. This was quickly identified (Lee et al., 1966) as PGA₂. Subsequently PGE₃ was shown to be the most abundant PG in rabbit renal medulla (Daniels et al., 1967) and PGF₂α also occurred in significant amounts (Lee et al., 1967). The facile conversion of PGE₃ to PGA₁ (and PGE₃ to PGA₁) by nonenzymatic dehydration under mildly acid conditions makes it difficult to determine how much PGA₁ occurs normally in the kidney as compared with the amount of PGE₃ which is converted to PGA₁ during the isolation. PGA₁ has been isolated from human seminal fluid (Hamberg & Samuelsson, 1967) where it is considered to be a normal component and not an artifact of the isolation procedure. Vasodepressor lipids have been isolated from human kidneys and concentrations of a PGE₃-like lipid ranging from 40 to 234 ng-equivalent/ml were detected in the renal venous blood of hypertensive patients but none was detected in samples from normotensive subjects (Edwards, Strong & Hunt, 1969). Recently, McGiff et al. (1970) have shown that angiotensin II induced the release of PG-like substances in dogs and suggested that an alteration of the balance between pressor substances (renin, PGF₂α) and depressor substances (PGE₃, PGA₁) may determine the development of renal hypertension. The neutral antihypertensive lipid of the renal medulla (Muirhead et al., 1967) may also be a factor in this balance.

Irrespective of their physiological occurrence and function, the potent vasodepressor and natriuretic activities of the PGA compounds made them attractive candidates for clinical evaluation in the renal-cardiovascular field. Also, in contrast to the PGE and PGF compounds, the PGAs are not quickly metabolized and inactivated by the lungs (McGiff et al., 1969). In early studies using purified PGA₂ isolated from rabbit kidneys, Lee (1967) reported that in dogs and in a human patient with essential hypertension PGA₂ caused a short-term hypotensive action and marked diuresis.

Current clinical studies are being carried out with PGA₁ because it was more readily available as a pure crystalline entity than PGA₂ and its biological properties appeared to be equivalent to those of PGA₂. Carr (1970) reported that PGA₁, administered by infusion at the rate of 0.48–1.32 μg/kg/min to five patients with mild essential vascular hypertension, resulted in increased cardiac output and renal blood flow, reduced blood pressure and decreased peripheral resistance. The renal fraction of the cardiac output was reported to increase dramatically. There was enhancement of free water clearance and decreased solute free water clearance in association with a sodium diuresis. In spite of the significant drop in mean arterial pressure, no change in plasma renin activity was detected. Christlieb et al. (1969) have reported briefly on the administration of PGA₁ to six hypertensive patients by i.v. infusion at rates varying from 0.3 to 1.2 μg/kg/min for 30–60 min. Blood pressure was lowered during the infusions, but the magnitude of the response varied with the individual. They reported that post-infusion rebound of the blood pressure was common and at times severe. Fichman (1969, 1970) administered PGA₁ to more than thirty-five patients (normals, hypertensives, hyponatremics, cirrhotics, anephric) by infusion at rates varying from 0.03 to 5 μg/kg/min. His studies were concerned mainly with the natriuretic action of PGA₁ under various circumstances. Greater augmentation of urinary sodium excretion occurred when PGA₁ and vasopressin (ADH) were infused at the same time. The most pronounced natriuretic response occurred in a cirrhotic patient with ascites in whom urinary sodium increased many fold. He interpreted his findings as suggesting that PGA₁ failed to alter the effect of ADH on water excretion but the natriuretic effect of PGA₁ was potentiated by ADH infusion, and the vasodepressor effect of PGA₁ was enhanced in anephric states.

Some details from the study of Westura et al. (1970) will serve to illustrate the antihypertensive and haemodynamic effects of PGA₁ in patients with essential hypertension. The study with six patients was divided into three 15-min periods. After the first 15-min which served as control, PGA₁ was administered by i.v. infusion at the mean rate of 1.0 μg/kg/min for 15 min (Period I). This was followed immediately by a 15-min period (Period II) during which the infusion-rate was increased to a mean rate of 2.0 μg/kg/min. During Period I there was an initial rise in sodium excretion and urine flow. This was followed quickly by a progressive fall in systemic blood pressure and a drop in peripheral resistance. There was a slight rise in stroke-volume index and in cardiac index, but a reflex increase in heart rate of from 72 ± 2 to 96 ± 3 beats per
minute (Figs. 2–5). During Period II with the infusion of 2 μg/kg/min a further small decrease in systolic blood pressure was recorded but no further lowering of diastolic pressure occurred. The heart rate continued to increase while the cardiac index decreased slightly. Urinary flow fell to a mean value which was higher than control but significantly lower than that observed during Period I. Changes in sodium excretion paralleled those of urinary flow. Potassium excretion (Fig. 6) was elevated during the 1 μg/kg/min infusion period, but decreased to control levels during the period of higher infusion rate. According to Lee and his associates (Westura et al., 1970) they did not detect a direct effect of PGA₁ on cardiac performance. They believe that the mechanism of anti-hypertensive action is 'by direct peripheral arteriolar...
dilation leading to a fall in peripheral resistance and a decline in systemic arterial blood pressure accompanied by a compensatory increase in cardiac index which is almost entirely the result of a reflex tachycardia.

It should be kept in mind that Lee and others have shown that the PGA compounds are perhaps the most potent natriuretic agents known in that they are effective at concentrations of the order of 0.1 ng/ml of renal arterial blood. When administered to man at low infusion rates of 0.1–0.3 μg/kg/min, rates which do not affect arterial blood pressure, renal blood flow, urinary sodium and potassium excretion, urine flow and free water clearance all rise significantly. At higher infusion rates, as shown above, the effects are reversed with renal plasma flow, urine flow, and electrolyte excretion falling to control values. Neither the role of these compounds in the physiological regulation of blood pressure, nor their place in the treatment of pathological conditions is clear at this time. However, available information indicates that they are worthy of further study and especially if long-acting, orally-active forms can be prepared, general therapeutic use may become feasible.

**Induction of labour and therapeutic abortion**

For many years clinicians had known that during menstruation the human uterus extruded the disintegrated endometrium by means of powerful coordinated contractions, but it was not until 1963 that the ‘menstrual stimulants’ presumably responsible for this action were identified as PGE_2_ and PGF_2α_ (Eglinton et al., 1963). When pure prostaglandins became available, numerous investigations were conducted on the influence of these compounds on human myometrium in vitro. Reports of the results have been somewhat conflicting, but in general it appeared that PGEs inhibit and PGFs stimulate activity in the non-pregnant human myometrium in vitro. However, in the human pregnant myometrium in vitro, Embrey & Morrison (1968) found that while the lower segment myometrium was relatively unresponsive, marked responses were observed with the upper segment and both PGFs and PGEs exhibited the stimulatory effects.

Karim and his co-workers demonstrated the presence of several PGs in human umbilical cord, human amniotic fluid and human decidua obtained at term (Karim & Devlin, 1967). High levels were found in amniotic fluid only from patients in spontaneous labour. They showed also that PGF_{2α} appeared in maternal venous blood in variable amounts during labour and that the concentration increased with progression of labour. A striking correlation between PGF_{2α} concentration and the contraction was noted. Blood levels rose during the period immediately before a labour contraction, were highest during the contraction, fell sharply immediately after the contraction and were usually undetectable between contractions.

With these findings suggesting a physiological role of PGF_{2α} in parturition, Karim and associates proceeded with the clinical investigation of the use of infusions of this prostaglandin to induce labour at or near term. A recent report (Karim et al., 1969b) describes their experience in thirty-five cases. PGF_{2α}, given by i.v. infusion at the rate of 0.05 μg/kg/min (1/40 of the rate found previously to be well-tolerated in men and one non-pregnant woman), stimulated uterine contractions to a pattern of uterine activity very similar to that of normal labour with complete relaxation between contractions. Hypertonicity was not encountered and the contractions were well spaced. In most cases contractions commenced 15–20 min after the infusion was started. Infusion was continued until labour was induced as determined by the position of the foetal head, strong regular contractions at 2–3 min intervals and by a cervical dilatation of 6–8 cm. Upon stopping the infusion, the uterus continued to contract regularly leading to successful delivery. In the twenty-nine patients in whom labour was successfully induced with a single infusion, the infusion time varied from 1 to 11½ hr. The average infusion delivery interval in thirty-three successful inductions was 9 hr 35 min. All babies delivered alive showed immediate spontaneous respiration and no discernible abnormality was noted.

In the latest report available from Karim et al. (1970), i.v. infusions of PGE_2_ were used to induce...
labour in fifty women at or near term. The infused dose was approximately 1/6 that of PGF_{2a} or 0.5 µg/min. Using a Palmer slow infusion pump a patient received between 0.005 and 0.01 µg/kg/min. The uterine activity produced by this treatment resembled that of normal spontaneous labour and no unphysiological increase in uterine tone was observed. Labour was successfully induced in all fifty cases. The average infusion time was 5.5 hr and the average infusion-delivery interval was 10 hr. The infusions produced no discernible foetal difficulties and had no effect on maternal blood pressure. The only side-effects reported were headache in one patient and vomiting in another.

Embrey (1969) reported observations made in fifteen patients in late pregnancy and five in early pregnancy undergoing i.v. infusion of prostaglandins. Six patients at or near term received PGFs (PGF_{2a}, one patient; PGF_{2b}, five patients) at an infusion rate of 2–8 µg/min. (ca. 0.02 to 0.14 µg/kg/min). Definite stimulation of uterine contractions was demonstrated in two cases and less marked or doubtful increase in contractility reported in four. The maximum infusion time was 80 min and the maximum total dose 200 µg. Contractions, which began within 15–30 min of infusion, continued long after cessation of infusion and diminished slowly. With two of the patients labour became clinically established within a few hours and one was already in labour at the beginning of the experiment. Labour ensued within 48 hr in two of the remaining three patients and after surgical induction in the other. In a parallel study with nine patients in late pregnancy PGEs were administered using the same infusion dosage regime. One patient received PGE_{1} and eight received PGE_{2}. The threshold dose was judged to be ca. 2 µg/min and dosage in the range of 2–6 µg/min induced marked increases in both frequency and amplitude of contractions. Hypertonus was observed in only one instance at the highest dose used (8 µg/min). With one exception labour was established within a few hours of the infusion and within 48 hr with the one exception. At these doses, even with the PGEs, no changes in blood pressure or pulse rate and no subjective side-effects were observed.

The effects of PGs on uterine contractility were determined in five early pregnancy cases involving patients recommended for termination of pregnancy. Evacuation of the uterus was performed within 24 hr of the infusion regardless of the response produced by prostaglandin treatment. Using the same infusion rate (2–6 µg/min), Embrey reported that the sensitivity of the myometrium appeared to be at least as high as in late pregnancy. PGE_{2} produced a more pronounced effect than PGF_{2a}. In contrast to the experience in late pregnancy, the response in early pregnancy was characterized by an increase in tone as well as stimulation of contractions.

PGF_{2a} interrupts early stages of pregnancy in rhesus monkeys (Kirton, Pharriss & Forbes, 1970a) and laboratory rodents (Gutknecht, Cornette & Pharriss, 1969). Kirton, Pharriss & Forbes (1970b) subsequently reported both PGE_{2} and PGF_{2a} terminated pregnancy when administered to monkeys either subcutaneously or intravenously between 30 and 41 days after conception. Increased uterine tone and contractions of about 60 mmHg occurred at a frequency of three per min within 10 min after starting an infusion of PGF_{2a} at a rate of 60 µg/min. PGE_{2} was effective by infusion at 8 µg/min. Plasma progestin concentrations declined 24–48 hr after initial administration.

Bygdeman et al. (1970) studied the effects of single i.v. injections of PGF_{1a} and PGF_{2a} in thirteen women in mid-pregnancy and one at the thirty-sixth week of pregnancy. They reported that the threshold dose of PGF_{1a} for production of a stimulating effect predominant in elevation of tone was between 200 and 500 µg and ca. 100 µg for PGF_{2a}. These authors also reported that i.v. infusion of PGF_{2a} at a constant rate of 3 µg/min (roughly equivalent to the 0.05 µg/kg/min rate used by Karim) had no effect on uterine motility, but they did not report the duration of the infusion or the stage of pregnancy of the patient. More recently this group (Roth-Brandel et al., 1970) reported results of a study in which i.v. infusion or repeated subcutaneous injections of PGE_{1} or PGF_{2a} were given to eleven women admitted for therapeutic abortion in the thirteenth to the eighteenth week of pregnancy. Both methods of administration induced uterine hypertonicity, which diminished slowly during treatment, and at the same time strong, somewhat labour-like, contractions. The effect lasted 1–2 hr and was normally sufficient to cause cervical dilatation leading to termination of pregnancy in three of the eleven women. Side-effects of nausea (with PGE_{1}) and diarrhoea (with PGF_{2a}) were observed in some patients in high doses. The authors expressed a preference for PGF_{2a} for this purpose. The latest report from this group (Wiqvist & Bygdeman, 1970) described their findings using i.v. infusions of PGF_{2a} at rates of 13–360 µg/min in seven women in the eighth week of pregnancy or earlier and in five women in the twelfth to sixteenth week. With those in the early stages of pregnancy bleeding started within a few hours after initiation of infusion followed by partial or complete expulsion of the conceptus within 2 days. Abortion was accomplished in three of the five cases of women in the twelfth to sixteenth week of pregnancy. Again the side-effects of diarrhoea or vomiting occurred but disappeared on reducing the infusion rate. It was
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noted that the abortive mechanism differed depending on the stage of pregnancy.

Karim followed his studies of induction of labour at term with an investigation of the use of PGF2α for therapeutic abortion. A recent report (Karim & Filshie, 1970) describes successful results in fourteen of fifteen cases using i.v. infusion of PGF2α at the rate of 50 μg/min until abortion was complete. Diarrhoea occurred in seven of the women in this series, three of whom also vomited. These were the only side-effects noted and they were not severe. These authors point out that there are both qualitative and quantitative differences in the response of the early pregnant uterus to PGF2α compared with those at term. In the latter situation i.v. infusion of 4 μg/min stimulated uterine contractions which were regular and rhythmical without increase in resting tone. On the other hand, during the first and second trimester of pregnancy an infusion rate of the order of 50 μg/min was required to stimulate the uterus. The initial effect was hypertonus and this was followed by rhythmic

Fig. 7. Effect of 0.05 μg/kg/min of prostaglandin F2α infusion on uterine activity of a pregnant woman aged 22, gravida 2, at 38 weeks gestation. Membranes had ruptured prematurely 36 hr before the start of the infusion. The infusion was given for 34 hr. The cervix (Cx) at the end of this period had dilated to 6 cm. A live baby weighing 2812 g was delivered 4 hr 50 min after stopping the infusion. (From Karim et al., 1969b). Reproduced by permission of the Editor, Journal of Obstetrics and Gynaecology of the British Commonwealth.)
contractions. Typical records of PGF\textsubscript{2α}-induced uterine activity in these two situations are shown in Figs. 7 and 8.

The three groups whose work is summarized briefly here all commented favourably, but with understandable caution, on the possible advantages of infusions of prostaglandins, particularly PGF\textsubscript{2α} and PGE\textsubscript{2}, over currently accepted methods for inducing labour at term and for therapeutic abortion. Compared with oxytocin, which acts quickly, the prostaglandins are notably slow in action, and their effect persists after infusion is stopped. Control of the action is readily achieved by the rate of infusion. Furthermore, the uterus in early pregnancy is relatively insensitive to oxytocin. The results to date, in the words of Karim, '... reinforce the possibility that prostaglandins may have a physiological role in parturition, and further suggest that prostaglandin F\textsubscript{2α} may represent a potentially valuable addition to the armamentarium of the obstetrician.' (Karim et al. 1969b). In the light of the more recent reports, one might also expect PGE\textsubscript{2} to be included in this category.

**Fertility control**

Because the prostaglandins were originally discovered in human seminal fluid and because their concentration in this fluid is the highest known in nature, it is not surprising that as early as 1947 Asplund suggested a correlation between total prostaglandin concentration in human seminal fluid and degree of fertility. Considering the complexity of the problem with thirteen prostaglandins being present and each with different biological action, it is also not surprising that 22 years were required to get meaningful support for Asplund’s suggestion. The analysis and quantitative determination of these compounds required methods which have only recently been devised (Bygdeman et al., 1969). Results of a study of a total of 137 different semen samples obtained from men with documented normal fertility, from men in infertile marriages of nonexamined origin and from men in ‘functionally’ infertile marriages indicate with statistical significance that the concentration of PGEs in human seminal fluid is of importance for normal fertility (Bygdeman, 1969). Semen samples from 40% of the men in functionally infertile marriages had a PGE content of less than 15 μg/ml whereas those from men of normal fertility had an average PGE content of 55.2 ± 20.2 μg/ml and none had a content of less than 15 μg/ml. Bygdeman concluded that determination of PGE content of seminal fluid may be of relevance in routine investigation of functionally infertile marriages.

The antifertility potential of the prostaglandins

![Figure 8](image_url)
seems in the light of current knowledge to rest mainly on a suggested luteolytic action of PGE$_{2a}$. This is, however, a very new area of research and the findings should be regarded as preliminary. In the normal ovarian cycle it is known that after the follicle develops and matures an ovum is discharged and a corpus luteum is formed. When the ovum is impregnated the corpus luteum continues to grow and to secrete the hormone progesterone. If fertilization does not take place, progesterone secretion stops, the corpus luteum regresses and in woman and primates menstruation occurs. The events leading to the development of the corpus luteum are known to be under the control of pituitary hormones and are relatively well understood, but the mechanism leading to regression of the corpus luteum when pregnancy does not occur remains obscure. There is evidence suggesting that the uncharacterized factor involved is produced by the uterus. For example, in species with a bicornuate uterus, if only one uterine horn is removed, the corpora lutea on that side persist, but those in the opposite ovary regress.

As a working hypothesis, Pharriss & Wyngarden (1969) proposed that PGE$_{2a}$ be considered as the missing factor which should meet the following requirements: (1) be produced in the uterus, (2) permit unilateral effects on the ovary, and (3) have properties consistent with luteal regression. Pickles and his co-workers (Eglinton et al., 1963) had already demonstrated that PGE$_{2a}$ was formed in the uterus and discharged in the menstrual fluid. Considering the second requirement, it was known that in most, if not all, species there is no direct vascular connection between the uterus and the ovary, but venous drainage from the ovary is shared with the uterus. Pharriss suggested that restriction of venous outflow from the ovary might lead to relative ovarian ischemia, limitation of substrates for hormone synthesis and/or accumulation of metabolites in such a fashion as to meet the third requirement. As related earlier, DuCharme et al. (1968) showed that in the dog some of the cardiovascular actions of PGE$_{2a}$ were probably secondary to venous constriction. Therefore, it seemed possible that uterine PGE$_{2a}$ could impede utero-ovarian vein flow and thereby depress luteal metabolism.

In experiments designed to test this hypothesis 0.1 or 0.2 mg PGE$_{2a}$ reduced venous outflow as assessed via a cannula inserted into the utero-ovarian vein of rats and rabbits (Pharriss, Cornette & Gutknecht, 1970). Investigations to detect a possible luteolytic action of PGE$_{2a}$ were carried out in animals treated to induce a persistent corpus luteum (Pharriss & Wyngarden, 1969). PGE$_{2a}$ was infused at 1 mg/kg/day via the uterus or the right heart into pseudopregnant rats on days 5 and 6 of pseudopregnancy. The ovaries were removed and determination of the progestogen content revealed that progesterone levels were decreased and concentrations of its metabolite, 20α-dihydroprogesterone, were increased. PGE$_{2a}$ administered subcutaneously to pseudopregnant rats shortened the pseudopregnancy to 7 days from a normal of 14 days. However, addition of PGE$_{2a}$ to rat ovaries incubated in vitro did not decrease the rate of progestogen synthesis. The pituitary did not seem to be involved because when pseudopregnancy was maintained in hypophysectomized rats by prolactin administration, PGE$_{2a}$ still decreased the ratio of ovarian progesterone to its metabolite. These and similar animal experiments supported the concept of an indirect mechanism for local luteal control by uterine tissue and an indirect effect of PGE$_{2a}$ on the ovary.

Since progesterone from a persistent corpus luteum is necessary for maintenance of early pregnancy, early regression of the corpus luteum would prevent nidation of fertilized ova and establishment of pregnancy. When PGE$_{2a}$ was given at appropriate times after mating it either prevented or reduced the incidence of pregnancy in mated rats, rabbits (Gutknecht et al., 1969), and monkeys (Kirton et al., 1970). Exogenous progestogen in the form of medroxy-progesterone acetate (Provera,* Upjohn) protected rats against the antinidatory action of PGE$_{2a}$ (Gutknecht et al., 1969) presumably because it replaced the progesterone lost when the corpus luteum regressed. Early pregnancy in the monkey is associated with a sustained elevation of plasma progesterone. When 30 mg of PGE$_{2a}$/day was administered subcutaneously for 5 days and injections were initiated on day 11, 12 or 13 postovulation of fertile cycles, plasma-progesterone levels fell promptly to nearly undetectable levels and menstruation occurred shortly thereafter. Several of the treated monkeys were mated again and normal pregnancies ensued (Kirton et al., 1970a).

Studies on the effect of PGE$_{2a}$ on corpus luteum function in women are apparently in progress, but no details have been published. However, Wiqvist & Bygdeman (1970) reported that preliminary experiments on non-pregnant women 'show that vigorous uterine contractions and menstrual-like bleeding may be induced also during the secretory phase of the cycle by infusion of PGE$_{2a}$. The eighteenth to nineteenth day of the cycle, when implantation of the blastocyst takes place or 2-4 days following the first missed menstrual period might even be more vulnerable periods to prostaglandin administration than later stages of pregnancy.' It seems likely that the evaluation of the

*Registered trade name.
antifertility potential of the prostaglandins will be vigorously pursued.

**Bronchodilator activity**

Rosenthal et al. (1968) reported that i.v. administration of PGE₂ at doses of 4–8 µg/kg completely prevented bronchoconstriction induced in anaesthetized guinea-pigs by histamine, serotonin, acetylcholine or bradykinin. This action of PGE₂ was not influenced by bilateral vagotomy, adrenalectomy, double pithing or pretreatment with reserpine or pronethalol. PGE₂ administered in aerosol prevented bronchoconstriction induced by aerosols of histamine in normal and in horse serum-sensitized guinea-pigs. In this species, PGE₂ was reported to be as active a bronchodilator as isoprenaline but with shorter duration of action. Other experiments indicated that PGE₂ caused considerably greater bronchodilation in the monkey than in the dog. This differed from isoprenaline which was equipotent in both species. Large, Leswell & Maxwell (1969) have compared the bronchodilator activities of aerosols of PGE₁ and isoprenaline in the anaesthetized guinea-pig and found PGE₁ to be 10–100 times more active than isoprenaline. However, by i.v. administration PGE₁ was slightly less potent than isoprenaline. They found that the bronchodilator responses to aerosols of isoprenaline could be partially or completely inhibited by propranolol, but there was no inhibition of the responses to aerosols of PGE₁. Since severe cardiovascular disturbances have been reported in man particularly following over-doses of sympathomimetic drugs such as isoprenaline, these authors recommended studies of the bronchodilator activity of PGE₁ aerosol in man.

Cuthbert (1969) recently reported the results of a preliminary study on the comparison of the actions of PGE₁ and isoprenaline in healthy and asthmatic volunteers on timed forced expiratory volume in one second (FEV₁). In addition to measuring FEV₁ by a Vitalograph, blood pressure, pulse rate and ECG were monitored. Inhalation of aerosols containing PGE₁ as the free acid proved irritating to the upper respiratory tract, but the neutral triethanolamine salt of PGE₁ was tolerated with little or no irritant effect in both normal and asthmatic volunteers. A blind comparison was made between metered doses of the triethanolamine salt of PGE₁ (55 µg), isoprenaline sulphate (550 µg) and placebo in five asthmatic subjects. The results indicated that PGE₁ caused an increase in FEV₁ comparable in degree and duration to that of isoprenaline. No change was noted in blood pressure, pulse rate or ECG in any of the patients. Isoprenaline produced its maximum effect in 3 min in four of the five subjects in contrast to 30 min for PGE₁ which maintained higher FEV₁ levels for a longer period, but there appeared to be little difference in the overall duration. Cuthbert concluded that these results suggest that aerosol administration of PGE₁ can cause substantial reduction in airways obstruction in asthmatic patients and that the relation of the prostaglandins to the function of respiratory smooth muscle merits further investigation.

**Nasal vasoconstrictor activity**

Although the prostaglandins are usually considered to be vasodilating substances, some instances of vasoconstrictor activity have been reported. An interesting example with some possibility of practical application is found in the work of Stovall & Jackson (1967) who reported that prostaglandins induced a constriction of the blood vessels of the nasal mucosa in dogs. PGE₁, PGE₂, PGA₁, PGF₁α and epinephrine were injected into a carotid artery and the resistance offered by the nasal passage to a constant stream of humidified air was recorded. The PGE₁ were equipotent (doses in the range of 5 µg/kg) to epinephrine, but their duration of action was more than seven times as long. PGA₁ and PGF₁α were about 1/100 as potent as the PGE₁. Individual dogs varied in their sensitivity to the prostaglandins but the consistency of the response, its correlation with a decrease in nasal mucosal temperature and its occurrence independent of a blood pressure change were cited as evidence of an actual vasoconstriction. The prolonged duration of increased nasal patency suggested the possibility of clinical use.

Jackson & Turner (1969) reported results of a preliminary study in human volunteers who received topical application of PGE₁ via an atomizer which was calibrated to deliver doses of 37, 50, 75 and 100 µg to one nostril. All the doses caused an increase in the patency of the nasal airway and a visible blanching of the nasal mucosa. The effect lasted from ½ hr at the lower dose to 10–14 hr at the 75 µg dose. The 100 µg dose caused subjective irritation in all subjects, but no change in pulse rate or blood pressure was noted. Ånggård (1969) also reported on the effects of topically applied doses of 10–15 µg of PGE₁, PGE₂ and PGF₁α on nasal airway resistance in seven normal men and women. Clear-cut increase in nasal patency was observed in four of the subjects following administration of the PGE₁, but no effect was noted with PGF₁α.

**Inhibition of gastric secretion**

As Horton (1969) pointed out, gastric secretion in response to a variety of secretagogues is believed to be mediated at least in some species via cyclic AMP formation and it would be expected that PGE₁ would inhibit gastric secretion by blocking adenylyl cyclase in the gastric parietal cells. While 'predictions' of the influence of prostaglandins on adeny
cyclase-mediated systems is not always straight forward (Butcher, 1969), it has been shown that in dogs (Robert, Nezamis & Phillips, 1967) and in rats (Shaw & Ramwell, 1968) prostaglandins inhibit gastric acid secretion induced by histamine or pentagastrin. Prostaglandins are known also to be released into the lumen of the rat stomach spontaneously and in response to various stimuli (Coccani, Pace-Asciak & Wolfe, 1968). They have been found in the gastro-intestinal wall of man (Bennett, Murray & Whyllie, 1968b), and they may play a physiological role in the control of intestinal motility (Bennett, Eley & Scholes 1968a). Orally administered PGE1 caused increased intestinal motility resulting in loose faeces in man (Horton et al., 1968). The possible significance of this in relation to the diarrhoea associated with some tumors has been considered (Sandler et al., 1968; Misiewicz et al., 1969).

Robert, Nezamis & Phillips (1967) have shown that PGE1, infused intravenously at rates of 0.5 to 1.0 μg/kg/min, markedly inhibited gastric secretion in dogs stimulated by food, histamine, pentagastrin, or 2-deoxyglucose. Maximum inhibition was achieved after 30–45 min, and was maintained throughout the infusion period. PGE2 inhibited gastric secretion stimulated by food or histamine, and the ED50, i.e., the dose reducing gastric secretion by 50%, was the same as for PGE1. PGA1 strongly inhibited food-induced secretion with an ED50 of 0.08–0.1 μg/kg/min. With all three compounds, gastric secretion rose and reached normal levels about 2 hr after the infusion was stopped. PGF2α (10 μg/kg/min) had no influence on histamine-induced gastric secretion.

Similarly, Robert, Nezamis & Phillips (1968) inhibited gastric secretion in rats with PGE1 given either by single subcutaneous injection or constant subcutaneous infusion. PGE1, infused subcutaneously, strongly inhibited both Shay ulcers and steroid-induced ulcers in rats. Regarding the mechanism of action, Jacobson (1970) concluded from studies in conscious dogs that PGE1 reduced secretion by a primary mechanism other than restriction of gastric mucosal blood flow. PGE1 did cause a decrease in blood flow, but this appeared to be the result rather than the cause of gastric secretory inhibition.

Thus far only very limited and preliminary studies in man have been reported. Horton et al. (1968) administered oral doses of 10–40 μg/kg to three human subjects and observed no inhibition of pentagastrin-induced gastric secretion. On the other hand, Wilson, Phillips & Levine (1970) have found that PGA1 infused at the rate of 0.5–1.25 μg/kg/min i.v. for 30 min decreased mean volume and acidity in eleven healthy volunteers after inducing gastric secretion by intravenous administration of sub-maximal doses of histamine.

References


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J. W. Hinman

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