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Control of Parturition in Man

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ABSTRACT

Human pregnancy differs from that of many other species in showing no abrupt changes in maternal levels of estrogen and progesterone at the start of labor. The fetus appears to play a relatively minor role in initiating parturition since mean pregnancy length is not markedly affected by major disorders of the fetal hypothalamus, pituitary or adrenals. Human pregnancy cannot be induced by estrogen treatment and corticosteroids are ineffective except in women beyond term. Prostaglandins are released into the maternal circulation and amniotic fluid during labor but there is no unequivocal evidence of their involvement in initiation of labor. However, there is circumstantial evidence favoring a local mechanism involving the fetal membranes and deciduum that controls prostaglandin release. These tissues contain glycerophospholipids enriched with arachidonic acid in the *sn*-2 position, phospholipase A_2 activity and prostaglandin synthetase. The local mechanism is readily activated by local trauma. It is proposed that the onset of labor is mainly the outcome of a genetically-determined maturational event in the amnion and/or chorion. The fetus itself and the mother may modulate, but rarely control, the time of birth.

INTRODUCTION

Despite the advances that have been made in recent years in the understanding of the physiology of the initiation of labor in various species, notably some of the ruminants and rodents, the mechanism in man remains enigmatic. Knowledge is fragmentary and not yet capable of being synthesized into a usable hypothesis incorporating each facet. It is clear that maintenance of human pregnancy is dependent on placental hormones and that the corpus luteum serves no useful purpose after the second month of pregnancy (Csapo et al., 1973). Thus luteolysis, which has an indispensible function in parturition in species such as the goat (Currie et al., 1973), rabbit (Fraenkl, 1905), and mouse (Harris, 1927), is not a component of the human system. Some species, of which the sheep and cow have been studied intensively, share with man an independence from corpus luteum function but differ from man in demonstrating readily measurable changes in placental hormone metabolism before labor starts. Man, along with nonhuman primates and guinea pigs (Heap and Deansley, 1966) appear to belong to a select group of 'placenta-dependent' mammals in which labor starts without the levels of hormones in the maternal circulation showing any clear indication of altered placental hormone metabolism.

In general, the reaction of investigators to the unaltered hormone levels in the maternal circulation at the start of labor has been either disbelieving ('evidence will be found if it is looked for correctly') or negative ('maternal hormone levels do not reflect placental hormone metabolism'). Little attention has been paid so far to the possibility that women begin labor in the absence of any abrupt change in the placental production of steroid or other hormones and that changes in target tissue responses rather than production may be the more important. This omission is rather surprising in view of the remarkable efficacy in inducing labor of quite minor local mechanical stimuli (e.g. stripping membranes) that would be unlikely to disturb placental function.

The dominant role of the fetus in initiating parturition in the sheep (a 'placenta-dependent' species) and the goat (a 'corpus luteum-dependent' species) has encouraged investigations to determine the extent to which the concept of fetal control of labor can be extrapolated to other species. This approach has been fruitful in some species but in the nonhuman primate as is apparent from the material presented by Dr. Lanman and in man as reviewed below, it seems that the part played by the fetus (as distinct from the conceptus as a whole) and in particu-

lar by the fetal hypothalamic-pituitary-adrenal system is a relatively minor one. The void left by so relegating the human fetus has yet to be filled by an alternative dominant system. Perhaps the onset of labor is truly controlled by a 'complex multifactorial system' in which no factor is dominant and each factor acts by itself so weakly as to be unidentifiable in isolation. Such a concept has little to commend it as a working hypothesis to be tested by investigation.

This paper reviews the present state of knowledge of the physiology of the onset of labor in man and considers possible mechanisms that are consistent with available evidence.

THE ROLE OF THE HUMAN FETUS

Labor occurs spontaneously in the absence of normal function of the fetal hypothalamic-pituitary-adrenal system but the length of pregnancy is likely to be disordered. In pregnancies complicated by anencephaly, the mean pregnancy length in patients in whom there is no polyhydramnios and no obstretic interference is approximately 40 weeks but the range is very wide (Honnebier and Swaab, 1973). Prolonged pregnancy has long been recognized as having a striking association with anencephaly but the fact that premature delivery is equally common has been noted only recently (Milic and Adamsons 1969). Generally, fetuses with adrenal hypoplasia but no other malformations are born at, or close to, term (Liggins, 1974). A family has been described in which siblings with adrenal hypoplasia were born at 42-43 weeks whereas unaffected siblings were delivered at term (O'Donohoe and Holland, 1968).

A prospective study of women at risk of premature labor revealed that a rise in plasma estradiol-17β preceded the onset of labor in those women delivering prematurely (Tamby Raja et al., 1974; Tamby Raja et al., 1975). A study of the adrenal weights in a group of premature infants dying soon after birth suggests that accelerated growth of the adrenals may be the cause of the rise in estrogen; Anderson et al. (1971) found that the adrenals were heavier when premature labor had no recognizable cause than when it followed a complication of pregnancy such as placenta previa or placental abruption.

A number of studies have measured corticosteroids in cord blood in an attempt to determine whether there is a prepartum rise in fetal levels. There is a progressive rise in plasma total corticosteroid (Smith and Shearman, 1974) and cortisol (Murphy and Diez d'Aux, 1972) with advancing gestational age at birth during the last month of pregnancy and a similar rise occurs in cortisol levels in amniotic fluid (Murphy et al., 1975; Fencl and Tulchinsky, 1975). However it is less certain that a sharp rise in fetal cortisol levels preceeds the onset of parturition. Leong and Murphy (1976) found that the mean umbilical arterial cortisol level was significantly higher than the umbilical venous level in infants born after both spontaneous and induced labors (Fig. 1). The mean arterial level in the group with spontaneous labor was higher than in the group with induced labor. Since maternal cortisol levels were similar in the two groups it seems unlikely that the higher arterial cortisol values associated with the spontaneous onset of labor can be accounted for by a more stressful labor. It is more likely that elevated cortisol levels in the fetus preceed the onset of labor. Similar studies reported by Talbert et al. (1973) were not in agreement with the above observations. They found no significant difference in cord plasma levels of cortisol when infants born after elective caesarean section were compared with those born after the spontaneous onset of labor.

If further work confirms a rise in fetal cortisol levels before the onset of labor, the possibility that it is causally related to the initiation of labor will need to be considered. There is no strong evidence at present to support such a relationship. Administration of large doses of glucocorticoids to pregnant women before term does not induce premature labor (Liggins and Howie, 1972). In pregnancies at least one week beyond term the injection of either dexamethasone 20mg (Mati et al., 1973) or cortisol sodium succinate 500mg (Nwosu et al., 1976) into the amniotic sac is followed by the onset of labor within 120 h in significantly more women than in a control group injected with vehicle only. Gamissans et al. (1975) using betamethasone 20mg found no difference in the injection-delivery interval of treated and control patients. It is of interest in relation to the role of oestrogens in parturition that women beginning labor after intra-amniotic corticosteroid treatment do so in the presence of markedly depressed plasma (Gamissans et al., 1975) and urinary (Nwosu et al., 1976) estro-

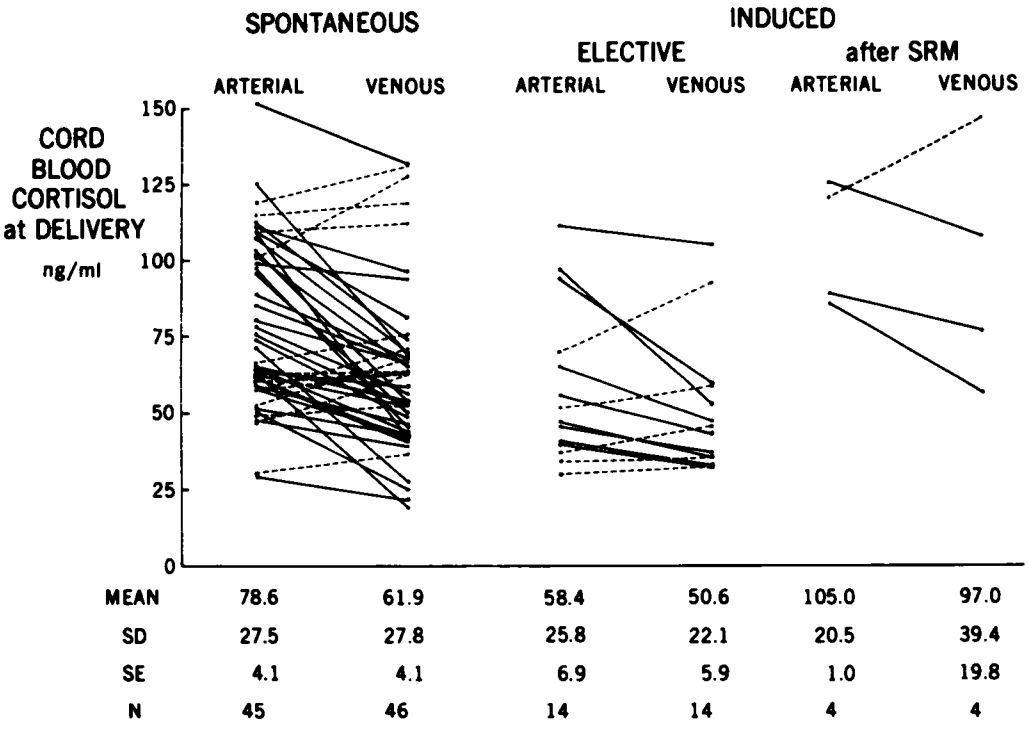

FIG. 1. Cord serum cortisol levels at delivery. SRM = spontaneous rupture of membranes. (From Leong and Murphy (1976) with permission of the Editor of the American Journal of Obstetrics and Gynecology).

gen levels (Fig. 2). The enormous dosage of corticosteroids given intra-amniotically, the inconsistent effect in inducing postterm labor and the absence of a response to treatment before term all suggest that cortisol is unlikely to serve as a physiological triggering mechanism in human labor. Possibly cortisol shares in a more complex endocrine trigger but is ineffective alone.

The case for an involvement of fetal cortisol in parturition would be strengthened by the demonstration of a means by which the action of cortisol could be mediated. There is no evidence of an action of cortisol on the human placenta similar to that seen in sheep. Maternal pregnanediol excretion is not lowered by corticosteroid treatment and estrogen levels are depressed (Oakey, 1970) rather than elevated as they are in sheep. The cause of the lowered estrogen production lies in a diminished secretion of dehydroepiandrosterone sulfate by the fetal adrenal (Simmer et al., 1974) whereas placental metabolism of steroids is unaffected by corticosteroid treatment.

The extremely low rate of estrogen production associated with placental sulfatase deficiency is associated with prolonged pregnancy and failure to respond to induction of labor in primigravidas but multiparas may begin labor spontaneously at or before term (France et al., 1973). The problems in sulfatase-deficient primigravid pregnancy appear to be associated with the state of the cervix which is small, hard and closed, resembling a nonpregnant cervix.

It is conceivable that the human adrenal stimulates labor through the combined effects of estrogen and cortisol since increased adrenal activity should lead to enhanced secretion of both cortisol and estrogen precursors. If such were the case, treatment with estrogens or cortisol alone might well be ineffective in inducing labor. We have compared the effectiveness in inducing labor of corticosteroids alone with corticosteroids combined with estrogen. In a controlled trial, women at or beyond 41 weeks of pregnancy were injected intra-amniotically with either dexamethasone 20mg, dexamethasone 20mg plus estradiol-17β 20mg, or vehicle. Significantly more women started labor with 80 h in the group treated with both steroids, but, nevertheless, the response was inconsistent and by 120 h only 70 percent of

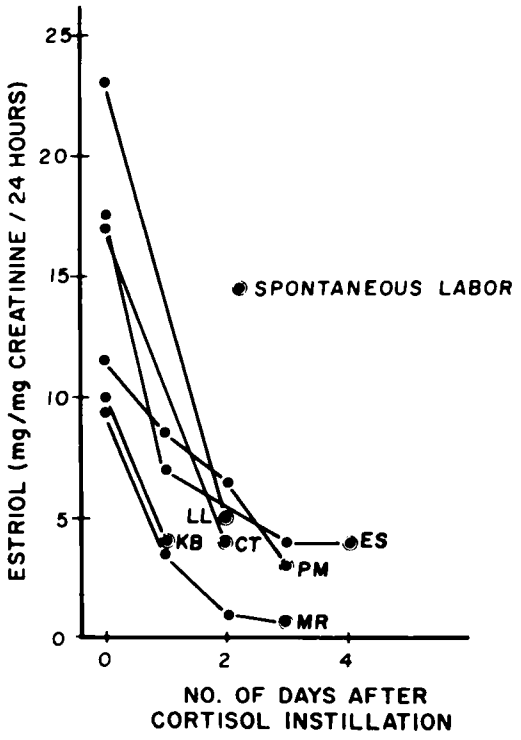

FIG. 2. Urinary estriol levels after intraamniotic instillation of 500mg cortisol sodium succinate. (From Nwosu et al. (1976) with permission of the Editor of Obstetrics and Gynecology).

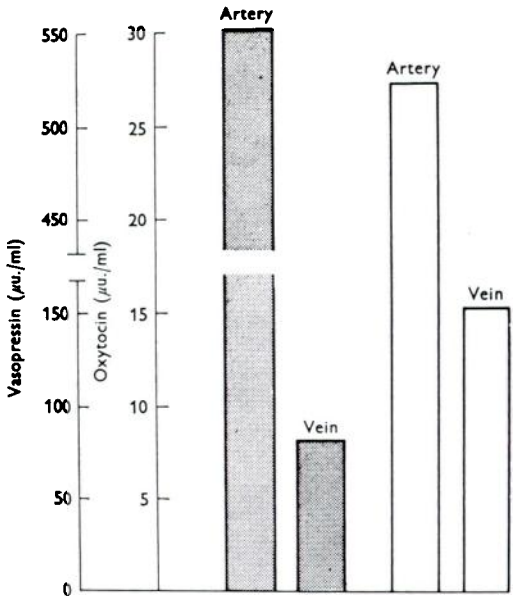

FIG. 3. Oxytocin (white bars) and vasopressin (shaded bars) concentrations in the umbilical artery and vein at the time of delivery in 38 women. (From Chard (1973) with permission of the Editor of Memoirs of the Society for Endocrinology).

the women had delivered (Liggins, unpublished observations).

Hormones other than those arising from the fetal adrenal cortex may have functions in parturition. Chard (1973) described high immuno-reactive oxytocin levels in cord blood at delivery compared to those in the maternal circulation and noted an umbilical arteriovenous difference, levels in the umbilical vein being the higher (Fig. 3). Arginine vasopressin also is elevated in cord blood during labor (Chard, 1973). Disordered pregnancy length associated with anencephaly could be explained by deficiency of the posterior lobe hormones. However, present evidence does not favor either fetal oxytocin or arginine vasopressin being involved in parturition. The concentrations of both hormones increase in fetal blood throughout the course of labor and there is a lack of evidence of increased levels at the time when labor starts. Furthermore, the human hemochorial placenta presents conceptual difficulties in postulating a route by which a hormone in the fetal circulation could reach the myometrium without first passing through the maternal heart and lungs after entering the blood of the choriodecidual space. There are similar problems in assigning a role to arginine vasotocin, an octapeptide found in fetal rats (Swaab, 1976). In addition, preliminary observations have failed to detect significant amounts of arginine vasotocin in the human fetus at term (Chard, 1976).

Notwithstanding these reservations about the likelihood of fetal hormones other than those secreted by the placenta entering the maternal circulation in amounts that could have actions on the myometrium, the possibility that fetal hormones could act on maternal tissues through a route other than the blood stream should not be overlooked. For example, consideration will be given in a subsequent section of this paper to hormones in amniotic fluid that might influence the metabolism of fetal membranes and decidua.

PROSTAGLANDINS

There is abundant evidence that prostaglandins have an important place in the physiology of human labor but as yet the question of whether prostaglandins are directly concerned

with the initiation of labor remains unresolved. Other speakers in this symposium have presented the evidence which shows that in many species increased synthesis and release of prostaglandins preceed labor and probably play an important part in its initiation. No such unanimity of opinion exists amongst human reproductive physiologists. Some physiologists liken the initiation of labor to a see-saw on one end of which is progesterone and on the other, prostaglandin (Csapo, 1973). The concentration of prostaglandin in the myometrium is envisaged as constant; prostaglandin-induced smooth muscle activation is prevented by progesterone. When the influence of progesterone is removed, prostaglandin expresses its presence and labor starts. Other physiologists consider the synthesis and release of prostaglandins to be suppressed, probably in part by progesterone, until labor is about to start when prostaglandins are synthesized in rapidly increasing amounts and activate the myometrium regardless of its hormonal status (Liggins, 1973). Although in species such as the sheep, the synthesis and release of prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) is known to be stimulated by estrogen and inhibited by progesterone (see preceeding paper by Dr. Thorburn) there is little evidence of these effects in women. The infusion of estradiol-17β into normal women at term stimulates uterine activity but there is no measurable increase in PGF in peripheral blood (Larsen et al., 1973). There are at least two reasons why such experiments are difficult to interpret. First, increased release of prostaglandin near the target organ may be sufficient to induce a response yet not to elevate levels in peripheral blood to the point where detection is possible by radioimmunoassay. Second, the role of highly potent intermediates in prostaglandin synthesis has yet to be determined. For the same reasons, interpretation of evidence relating to the place of prostaglandins in the initiation of labor is unsatisfactory.

Intuitively, one might well feel that prostaglandins play an important part in initiating labor. Not only is prostaglandin treatment able to stimulate labor or abortion that mimics the spontaneous event but prostaglandin inhibitors such as aspirin and indomethacin delay both the progress of induced mid-trimester abortions (Waltman et al., 1973) and the onset of labor at term (Lewis and Schulman, 1973). However, the third piece of evidence neended to establish prostaglandins as strong contenders for the place as the major stimulus to labor is missing; it has yet to be shown that the onset of labor is immediately preceeded either by increased release of prostaglandins or by enhanced responsiveness of the uterine tissues to prostaglandins. Detection of $PGF_{2\alpha}$ or PGE_2 in peripheral blood is a formidable task because of the low levels likely to be present. It has been estimated from studies of the kinetics of prostaglandin metabolism (Granstrom, 1972) and of production rates (Samuelsson, 1973) that the expected concentration of $PGF_{2\alpha}$ during pregnancy is about 2 pg/ml, a level well below the limits of sensitivity of radioimmunoassays and bioassays. Metabolites of $PGF_{2\alpha}$ which have relatively long half-lives in plasma and which are not formed during collection of blood samples offer a better prospect of studying changes in the rate of release of $PGF_{2\alpha}$. Gréen et al. (1974) assayed the major metabolite, 15-keto-13,14-dihydro-$PGF_{2\alpha}$, by GLC-mass spectrometry and found a small increase in peripheral plasma levels close to term and a sharp increase during active labor (Fig. 4). The concentrations of $PGF_{2\alpha}$ and PGE_2 in amniotic fluid show a similar pattern (Salmon and Amy, 1973; Keirse et al., 1974). In none of these studies has a rise in levels been clearly identified close to the onset of labor. The evidence that most strongly supports prepartum release of $PGF_{2\alpha}$ was reported by Hillier et al. (1974) who found

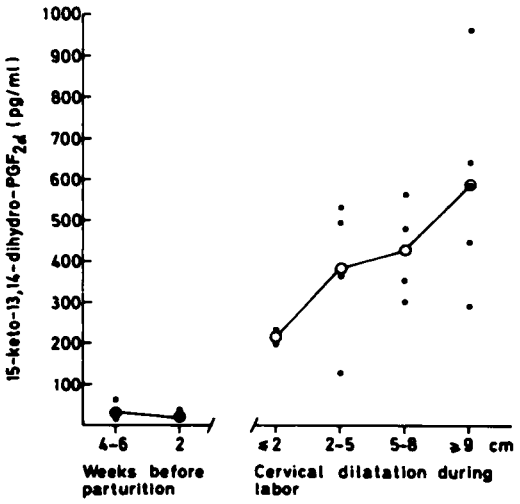

FIG. 4. Plasma levels of 15-keto-13,14-dihydro-$PGF_2\alpha$ during pregnancy and labor in the human. (From Gréen et al. (1974) with permission of the Editor of the American Journal of Obstetrics and Gynecology).

significantly higher concentrations of $PGF_{2\alpha}$ in amniotic fluid obtained in early spontaneous labor than in early induced labor although uterine activity in the latter group was greater.

The site of increased prostaglandin production in labor is uncertain. Evidence that it is released from the contracting myometrium is conflicting. Reports that the concentration of PGF in peripheral blood of women in spontaneous labor shows peaks corresponding in time with uterine contractions (Sharma et al., 1973; Challis et al., 1974) were not confirmed in a similar study in which 15-keto-13,14 dihydro-$PGF_{2\alpha}$ was measured (Greén et al., 1974). Assays of prostaglandins or their metabolites in serial samples of uterine vein blood obtained at caesarean section in laboring women have not been reported. As regards the initiation of labor, a myometrial source dependent on contractions for generation of prostaglandins is unsatisfactory for obvious reasons. Deciduum is favored as a source of prostaglandins because it may have the potential for prostaglandin release independently of uterine contractions. The possible role of decidua and fetal membranes in prostaglandin synthesis will be considered in a subsequent section of this paper.

Not only the rate of synthesis but also the rate of degradation could influence levels of prostaglandin in tissues. The enzyme 15-hydroxydehydrogenase is present in human placenta and chorionic membrane and it has been suggested that a high rate of degradation of prostaglandins by these tissues may have a physiological role in maintaining pregnancy (Keirse and Turnbull, 1976; Keirse et al., 1976; Keirse et al., 1974). However, there is no evidence of decreased activity at the onset of labor as would be expected if the enzyme contributed significantly to uterine activation.

MYOMETRIUM AND CERVIX

The successful accomplishment of the first stage of labor is dependent not only on the quality of myometrial contractions but also on the capacity of the cervix to distend sufficiently to allow the passage of the conceptus. In labor at term it is usual that these two components act in concert to the extent that dilatation of the cervix has usually been considered to be a consequence of myometrial activity alone. At the same time it has been clearly recognized that the cervix undergoes considerable changes in its physical properties prior to the onset of labor and that labor in the absence of these changes is likely to be protracted or unsuccessful. Since these cervical changes preceed active labor it is reasonable to consider them as part of the initiation process.

Activation of the Myometrium

The factors responsible for uterine activation are unknown. Indeed, the controversy is not yet resolved as to whether activation represents a release from inhibitory influences or a response to one or more stimuli. There is no convincing evidence in women of withdrawal of an inhibitor before labor starts. Equally, however, there is no convincing evidence of release of a uterine stimulant. On the whole, present opinion tends to favor a uterine stimulant mainly, perhaps, because of current interest in the prostaglandins.

Uterine Inhibitors

Progesterone concentrations in peripheral plasma show no change with the onset of labor (Shaaban and Klopper, 1973; Turnbull et al., 1974) (Fig. 5) nor is there evidence of significant changes in the concentration or distribution of progesterone in the myometrium. The levels of progesterone in myometrial tissue close to the placenta compared to non-placental areas, although elevated in the first trimester, show no significant differences at term (Runne-

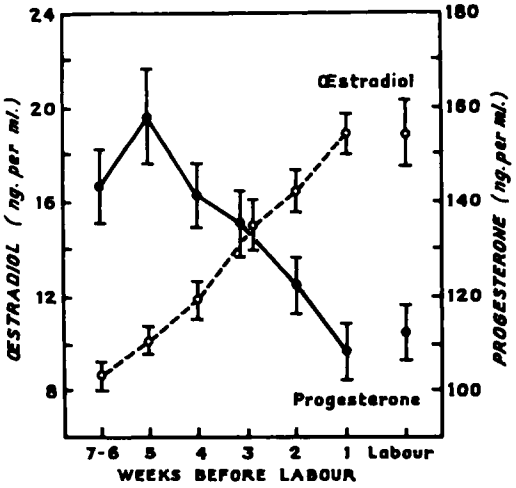

FIG. 5. Mean levels ±SEM of plasma progesterone and estradiol in 33 primigravidas during the 7 weeks before the spontaneous onset of labor and in the second stage of labor. (From Turnbull et al. (1974) with permission of the Editor of Lancet).

baum and Zander, 1971). Further studies, particularly of progesterone receptor-site concentrations in various parts of the uterine muscle, are needed before the possibility of changes in local concentrations of progesterone in the myometrium can be dismissed. But even were local changes observed, their significance would be impossible to assess in the absence of evidence of a direct inhibitory influence of progesterone on the human myometrium *in vivo*. There has been a consistent failure of attempts to inhibit uterine activity with large doses of progesterone or medroxyprogesterone whether administered intramuscularly, intravenously, intraamniotically or intramyometrially (Hendricks et al., 1961; Wood et al., 1963). This failure is understandable if progesterone receptors are fully saturated at normal plasma progesterone concentrations but it follows from this that a reduced influence of progesterone on the myometrium will occur only when the concentration of receptors falls or when progesterone is displaced from the binding sites; neither of these changes has been described. Interest is now turning to progesterone binding in uterine tissues other than myometrium where progesterone may take part in the regulation of prostaglandin biosynthesis (Schwarz et al., 1974).

Relaxin has passed through a long phase of obscurity since clinical traits of porcine relaxin in women in labor failed to show consistent effects. For several reasons, previous studies cannot be regarded as evidence that relaxin is of no importance in women. First, relaxin may be species-specific and porcine relaxin may be inactive in man (Bryant, 1972). Second, many of the clinical studies used doses that may have been inadequate (Slate and Mengert, 1960). Third, the method of quantifying responses in women in labor may have been inappropriate if relaxin has little effect (as is the case with the guinea pig) on the responsiveness of the myometrium to agents such as oxytocin and prostaglandin (Porter, 1972). Renewed interest stems from the development of a radioimmunoassay for human relaxin (Bryant, 1972) and it may now be possible to establish whether relaxin plays any part in the physiology of human parturition.

Some of the synthetic betamimetic amines such as ritodrine and salbutamol are remarkably effective in inhibiting labor (Landesman et al., 1971; Liggins and Vaughan, 1973) but there is no evidence that the uterus normally is strongly inhibited by endogenous cateholamines. The catecholamine content of the pregnant uterus is relatively low (Cha et al., 1965). Hypertensive pregnant women treated with large doses of the beta blocker, propranolol, are not prone to premature labor (G. C. Liggins, unpublished observations). Assays of urinary catecholamines have not revealed changes at the onset of labor although there is probably an increase in excretion of norepinephrine during labor (Goodall and Diddle, 1971; Kudo and Rouse, 1970). There is insufficient information at present to define the role of the nervous system and of catecholamines in human parturition. It seems unlikely that they play a major part in the initiation process but it is possible that neural mechanisms modulate uterine activity to the extent of influencing both the time of day when labor starts and the intensity of uterine contractions.

Uterine Stimulants

Evidence for the involvement of oxytocin in human parturition is conflicting. On the one hand, sensitive radioimmunoassays detect oxytocin in peripheral blood in the early first stage of labor in only about 10 percent of patients and measurements of intramammary pressure usually show no changes during labor (Cobo, 1968; Chard, 1973). The frequency of detection of oxytocin by radioimmunoassay increases as labor progresses and is maximal in the second stage. On the other hand, intravenous alcohol inhibits premature labor when the membranes are intact and the cervix is less than 3 cm dilated (Fuchs et al., 1967). The effect of ethanol has been attributed to inhibition of oxytocin release from the posterior pituitary. This proposal is supported by the observation that there was parallelism in oxytocin dose-response curves obtained before and during ethanol infusion in five out of ten women at term (Mantell and Liggins, 1970). The sensitivity of existing assays of oxytocin is insufficient to examine the effects of ethanol by direct means. Present evidence does not suggest that oxytocin in the maternal circulation is important in initiating labor but it is consistent with a role in the maintenance of established labor. There may be an interaction of prostaglandin and oxytocin since there is a progressive enhancement of oxytocin response during prolonged intravenous infusion of subthreshold doses of $PGF_{2\alpha}$ (Hutton and Liggins, unpub-

lished observations).

The acute effects of estrogen on the human myometrium are the subject of controversy. Jarvinen et al. (1965), Pinto et al. (1966) and Larsen et al. (1973) were able to stimulate uterine contractions but not labor by administering large doses of estrogen to women at term. These reports together with the finding that estrogen treatment caused a marked increase in uterine activity in a castrated woman (Moawad and Bengtsson, 1968) suggested that estrogen is oxytocic. Similar observations were made *in vitro* using rats or rabbits pretreated with estrogen (Melton and Saldivar, 1966; Csapo, 1969). The effect of estrogen appears to be to enhance propogation of electrical impulses over the muscle. However, estrogen applied directly to rat uterine strips in an organ bath abolishes electrical and mechanical activity (Melton and Saldivar, 1966). These apparently paradoxical results are explained in part by the effects of estrogen in reversing castration smooth muscle atrophy but an apparently oxytocic action *in vivo* remains unexplained. In view of recent work linking prostaglandin synthesis with estrogen, consideration should be given to the possibility that the effects of estrogen on propogation and contractility are mediated by prostaglandins.

Uterine stimulating effects of prostaglandins are considered elsewhere. Of the various other biological agents with oxytocic activities such as serotonin, norepinephrine, kinins and angiotensin II, none has been implicated in the initiation of labor.

Cervix

In the last few days or weeks of pregnancy the cervix changes from a long, firm, closed structure to one that is short, soft and distensible. The structural changes that accompany the altered macroscopic features have been described by Danforth et al. (1974). Compared to the non-pregnant cervix, the connective tissue of the postpartum cervix shows features that are consistent with disolution of the collagen framework. There is a slight increase in water content and a marked decline in the content of collagen and glycoprotein (Table 1). In addition to an absolute loss of collagen, the bundles are widely separated and probably are permitted to slide upon one another (Fig. 6). Marked changes are found in the ground substance of the postpartum cervix. The amount of glycosaminoglycans is greatly increased and their composition is changed. The nonpregnant cervix contains little uronic acid-free glycosaminoglycan (usually considered to be keratin sulphate) whereas the postpartum cervix contains a substantial amount. Glycoproteins are markedly reduced. In addition, Danforth et al. (1974) found in the dilated cervix a considerable quantity of an unidentified material, possibly a glycosaminoglycan, which is almost absent from the nonpregnant cervix.

Neither the source of the proteases and collagenases that must be responsible for the altered collagen structure of the softened cervix nor the stimulus to their activity is known. In mice, treatment with estradiol or relaxin induces loosening and scattering of the collagen fibrils (Leppi and Kennison, 1971). In women, there is some indirect evidence to suggest a relationship between estrogen and cervical softening. Prelabor cervical changes are normally occurring at a time when plasma estradiol is rising to maximal levels (Turnbull et al., 1974) (Fig. 5). In sulfatase deficient pregnancies with very low estrogen levels, the cervix may remain small, firm and closed (France et al., 1973). In the sheep, local application (Liggins et al., 1976) or arterial infusion (Fitzpatrick, 1976) of $PGF_{2\alpha}$ can cause softening and dilatation of

TABLE 1. Composition of glycosaminoglycans in human cervix (micromoles per gram of dry weight of defatted tissues). From Danforth et al. (1974).

Cervix	Hexosamines[a]	Uronic acid[b]	Galactosamine[c]	Keratin sulfate
Nonpregnant	14.6	10.7	9.9	3.9
Pregnant	38.9	7.7	17.5	31.2

[a]Hexosamine is contained in all glycosaminoglycans.

[b]Uronic acid is contained in all glycosaminoglycans except keratin sulfate.

[c]Galactosamine is contained only in chondroitins and dermatan sulfate.

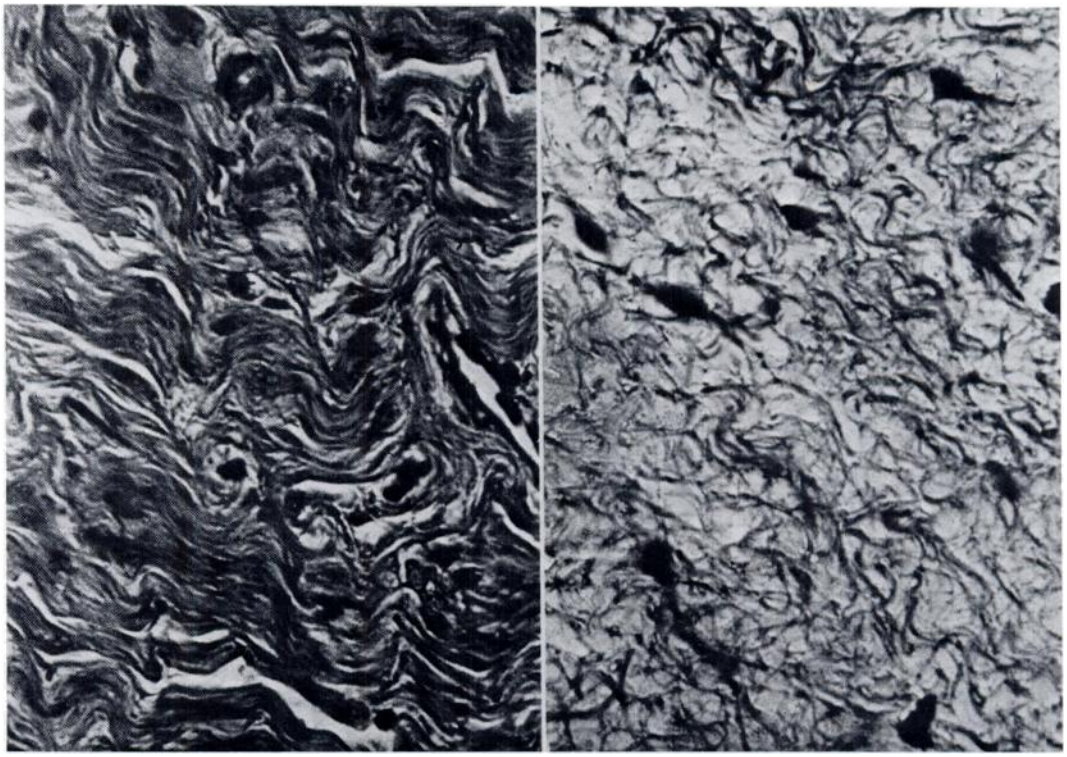

FIG. 6. Cervix approximately 1cm above plane of external os. Stained with Milligan's triichrome stain for collagen. On left, nonpregnant. On right, immediately postpartum. X835. (From Danforth et al. (1960) with permission of the Editor of the American Journal of Obstetrics and Gynecology).

the cervix and in women there are reports of 'ripening' of the cervix by means of prostaglandin treatment (Calder and Embrey, 1973; Weiss et al., 1975). In the latter studies, no attempt was made to assess the contribution that enhanced uterine activity might have made to the cervical changes. It is difficult to separate cervical and myometrial effects of prostaglandins since the continued administration of small doses of prostaglandins usually leads to an increase in uterine activity. However, in one study of 20 women at term in whom uterine activity was monitored during intravenous infusion of subthreshold doses of $PGF_{2\alpha}$, marked cervical changes were observed in the absence of uterine contractions in three patients (Liggins et al., 1976).

Certain clinical conditions suggest that myometrial activity and cervical changes can be dissociated under certain abnormal circumstances. On the one hand, strong uterine contractions may cause complete annular detachment of an unyielding cervix (Jeffcoate, 1952). On the other hand, the 'incompetent' cervix may dilate more or less completely in the absence of contractions.

Although we are almost completely ignorant of the physiological control of the pregnant cervix, two principles are clear. First, that cervical softening in prelabor must be explained in biochemical terms. And second, that an hypothesis for the initiation of human labor is incomplete unless it includes a satisfactory explanation for the structural changes in the cervix.

Mid-trimester Abortion

Some insight into the mechanisms of labor at term can be gained from induced midtrimester abortion in which the whole process of parturition is accomplished within 24 h at a time when pregnancy is at its most stable. A variety of techniques are effective in inducing abortion, a notable exception being oxytocin which fails to induce abortion unless given in massive doses late in the midtrimester (Burnhill et al., 1962). Mechanical (bougies and bags),

physical (hypertonic solutions of sodium chloride, urea or glucose), chemical (dilute formalin and Uter's paste), bacteriological (inadvertent amnionitis) and pharmacological (prostaglandins) agents placed intraovularly or extraovularly cause abortion with great consistency (see Gustavii, 1973 for review). Furthermore, the uterus of patients who fail to abort after such interventions is usually found to have become more responsive to oxytocin to which it responds with cyclical activity and abortion.

There is no agreement on the mechanisms involved in the initiation of induced abortions. Rapid expansion of amniotic fluid volume (Csapo, 1969) fetal death (Kovács, 1970) and placental damage (Weist et al., 1970) have all been proposed. Degenerative changes in the placenta in saline-induced abortions has been described (Wynn, 1965; Jakobovits et al., 1970) and may be the basis of the modest fall in the concentration of progesterone in maternal plasma at the time when uterine activity is established some hours after injection of the hypertonic solution (Csapo et al., 1969). Placental damage and a fall in progesterone production are less likely to result from methods of induction that invade only the extraovular space. In these circumstances, as well as when hyperosmolar or irritant solutions are placed in the amniotic sac, the tissues most vulnerable to damage are the fetal membranes and the deciduum. Marked degenerative changes in decidua have been described after intraamniotic injections of hyperosmolar saline (Gustavii, 1973; Vassilakos et al., 1973).

Gustavii (1973) suggested that the various methods of inducing abortion had in common as their mechanism of action the release of prostaglandins from the decidua. Experiments designed to substantiate the role of prostaglandin release have had a measure of success. Aspirin significantly extends the injection-abortion interval in nulliparous women treated with intraamniotic urea (Niebyl et al., 1976) and indomethacin has a similar effect in saline-induced abortion (Waltman et al., 1973).

Induced abortion cannot be regarded as an experimental model for spontaneous parturition at term. Nevertheless it serves a useful function in drawing attention to the possible importance of a local intrauterine system that may provoke parturition without fetal or placental participation.

DECIDUA AND FETAL MEMBRANES

Decidua and fetal membranes probably are able to synthesize prostaglandins and may be the source of prostaglandins that accumulate in amniotic fluid during labor. Sykes et al. (1975) found a low rate of synthesis of PGF and PGE when fresh deciduum or myometrium was incubated *in vitro* in a medium containing reduced glutathione. Addition of arachidonic acid or phospholipase A_2 (E.C.3.1.1.4) to the incubates increased PG production, particularly that of PGE. Keirse and Turnbull (1976) demonstrated synthesis of PGE during incubation of chorion but not of amnion. Chorionic membrane usually includes some decidual tissue (Gustavii and Brunk, 1972) which could be the site of prostaglandin production attributed to chorion. Further studies comparing the rates of decidual and chorionic production of prostaglandins under identical conditions are needed to resolve this question. The use of deciduafree chorion such as can be obtained from binovular twin pregnancies will be desirable.

The fetal membranes and deciduum are uniquely suited to prostaglandin production since all of these tissues contain glycerophospholipids that are highly enriched with arachidonic acid, the obligatory precursor of $PGF_2\alpha$ and PGE_2. Schwarz et al. (1975) noted that the 20 percent of the total fatty acid content of chorioamnion was arachidonic acid compared with 0.4 percent in maternal peritoneum. Deciduum is similarly enriched with arachidonic acid. The arachidonic acid content of the fetal membranes at term could meet many times over all the substrate requirements for prostaglandin synthesis in labor (Schwarz et al., 1975).

The incorporation into amnion phospholipids of arachidonic acid relative to palmitic acid has been studied *in vitro* by Schwartz et al. (1976b). Palmitic acid is the most abundant fatty acid of amniotic fluid and is not a precursor of prostaglandins. They found that arachidonic acid incorporated into phospholipids is contained mainly (53 percent) in lecithin and to a lesser extent (27 percent) in phosphatidyl ethanolamine. This distribution is similar to that of lecithin and phosphatidyl ethanolamine in term amnion (Pritchard et al., 1968). However, whereas the relative incorporation of palmitic acid and arachidonic acid into phosphatidyl ethanolamine is in accord with fatty acid composition, as described by Robert-

son and Sprecher (1968), the incorporation of arachidonic acid into lecithin greatly exceeds the amount expected from the latter's composition. This suggests that the turnover of arachidonic acid relative to palmitic acid is high in lecithin. The factors that regulate fatty acid turnover in fetal membranes and cause incorporation of arachidonic acid in preference to other unsaturated fatty acids are unknown. Hormones contained in the amniotic fluid need to be considered in this regard. Cortisol (Jolivet, 1972) prolactin and vasopressin (Manku et al., 1975) are all present in amniotic fluid and can induce marked changes in the permeability to water of the fetal membranes. In addition, amniotic fluid contains oxytocin and conjugated oestrogen. The membranes contain sulfatase activity that could liberate unconjugated oestrogens in the membranes and deciduum (Warren and Timberlake, 1962).

The pattern of fatty acid content of, and incorporation into, fetal membranes at various stages of pregnancy has not been described. However, the fatty acid composition of phospholipids in amniotic fluid described by Das et al. (1975) suggests that specific incorporation of arachidonic acid occurs late in pregnancy (Table 2).

The means of liberating arachidonic acid from storage in phospholipids must be available in a tissue that is to serve as an effective source of substrate for prostaglandin synthesis. Since arachidonic acid is contained mainly in the 2-acyl position of glycerophospholipids, a phospholipase A_2 is required for hydrolysis. Term amnion (Grieves and Liggins, 1976), chorioamnion and deciduum (Schultz et al., 1975) contain phospholipase A_2 activity that has specificity for phospholipids containing arachidonic acid (Schultz et al., 1975). The specific activities in the various tissues was compared by Grieves and Liggins (1976) who found the greatest activities in deciduum and amnion; the activities of chorion and myometrium were substantially less (Fig. 7). They found no differences between tissues obtained before and during labor.

In many tissues, phospholipases are lysosomal enzymes and their activity depends on release from the lysosome. This led Gustavii (1972) to propose a 'lysosomal theory' of parturition in which a key role in the initiation of parturition is attributed to lysosomes of the deciduum. According to Gustavii, the deciduum becomes rich in lysosomes which are maintained in a stable state by the presence of stabilizers particularly progesterone. The onset of labor or abortion is precipitated by labilizing influences that cause leakage of lysosomal enzymes, including phospholipase A_2, into the cytoplasm. The increased activity of phospholipase A_2 causes accelerated deacylation of phospholipids at the *sn*-2 position which leads in turn to the release of fatty acids including arachidonic acid. Since the synthesis of prostaglandins probably is not rate-limited by prostaglandin synthetase (Pace-Asciak and Wolfe, 1970), an increase in arachidonic levels results in increased prostaglandin production. The prostaglandin released from the deciduum is postulated as diffusing partly into the myometrium which it activates, and into the amniotic fluid where a rise in concentration is observed.

Evidence is accumulating to support this hypothesis. The lysosomes of decidual cells are unusually fragile and leak their contents when subjected *in vitro* to slight physical stresses (such as hypo- or hyperosmolar conditions) that have no discernible effect on other tissues (Brunk and Gustavii, 1973). Within two hours of injection of hypertonic saline into the amniotic sac, marked degenerative changes that preceed any fall in maternal progesterone levels are observed in the decidua parietalis (Vassilakos et al., 1974). Even an isotonic solution (0.9 percent NaCl) induces abortion when

TABLE 2. Arachidonic acid composition of lecithin and sphingomyelin of human amniotic fluid at different periods of gestation (Das et al., 1975).

Phospholipid	Duration of pregnancy			
	18–22 wk	27–33 wk	34–40 wk	Term labor
Lecithin	6.3 ± 0.1*	11.5 ± 0.2	0.8 ± 0.01	10.6 ± 0.1
Sphingomyelin	3.3 ± 0.07	1.5 ± 0.0	1.7 ± 0.06	30.4 ± 4.2

*Mean percent arachidonic acid ± SD.

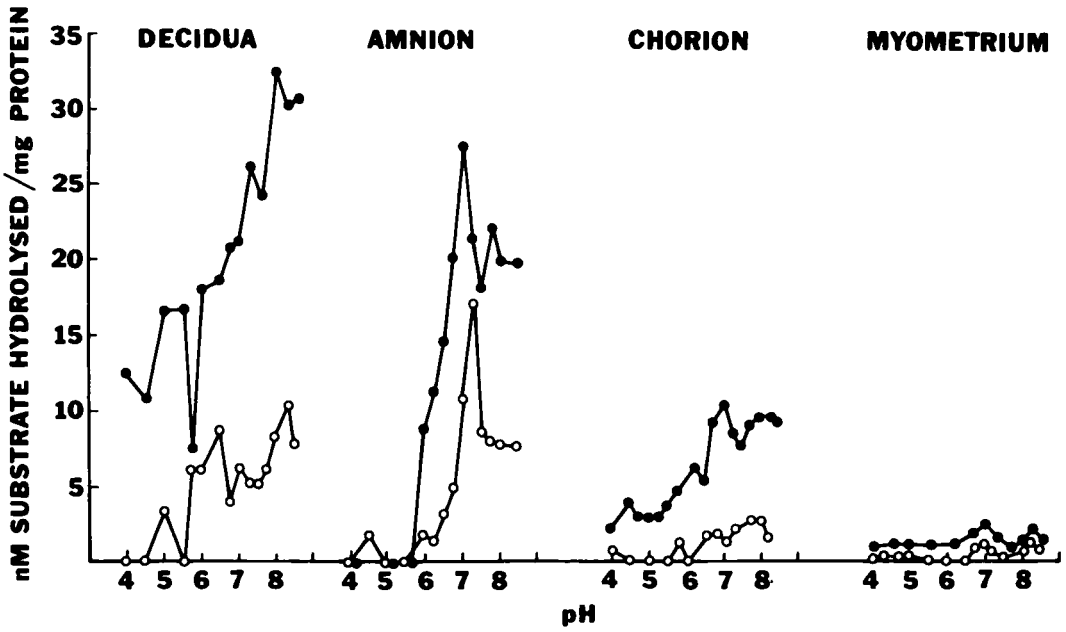

FIG. 7. Activity in human tissues of phospholipase A_2 according to pH. The tissues were obtained at caesarean section during labor. Phosphatidyl ethanolamine containing [^{3}H]-arachidonic acid at the *sn*-2 position was incubated at 37°C with crude lysosomal fractions. The amount of substrate hydrolyzed was calculated from the ratio of total counts in the reaction mixture to the counts in the purified fatty acid fraction. o———o 15 min incubation; •———• 2 h incubation.

injected outside the membranes (Gustavii, 1974). Decidual cells obtained at elective caesarean section at term show marked degenerative changes (Fig. 8) and signs of release of the lysosomal enzyme, acid phosphatase, into the cytoplasm (Gustavii, 1975). Thus, the first step in the biosynthesis of prostaglandins—the release of phospholipase A_2 from lysosomes—is active prior to the onset of labor or abortion. There is evidence also that the next step—the release of free arachidonic acid—is enhanced during labor. MacDonald et al. (1974) compared the concentration of free arachidonic acid in amniotic fluid from women before and during labor. They found a fourfold increase of both arachidonic acid and PGF. Other fatty acids increased less strikingly. The third step—conversion of arachidonic acid to $PGF_{2\alpha}$—has been demonstrated by MacDonald et al. (1974). Injection of 1.2g of potassium arachidonate into the amniotic sac induces abortion whereas oleate is inactive. The arachidonate-induced abortion is prevented by simultaneous ingestion of aspirin. These workers suggest that the large dose of arachidonate is needed because of metabolism of $PGF_{2\alpha}$ by the fetal membranes. Finally, the last step—activation of the myometrium by prostaglandin from within the uterus—is a well known effect of intra-amniotic or extra-ovular administration of $PGF_{2\alpha}$ or PGE_2.

Not only the deciduum but also the fetal membranes have features that make them particularly well suited to take part in the biosynthesis of prostaglandins. As already described, there are some reservations about the metabolic activities of the chorion because of its structural inhomogeneity but amnion is readily obtainable without contamination by other tissues. Studies of the amnion show it to be incapable of prostaglandin synthesis or degradation (Keirse and Turnbill, 1976) but in other respects it has several similarities to deciduum. The amnion, unlike the chorion, is an unusually fragile tissue, undergoing marked cell lysis during brief incubation (1 h) in 0.9 percent NaCl (Schwartz et al., 1976a). To maintain the structural and metabolic integrity of the amnion, incubation media closely resembling amniotic fluid are required (Fig. 9). Despite the small fraction of the amnion that is cellular, it is a highly metabolically active tissue (Schwartz et al., 1976a), the rate of glucose utilization exceeding that of muscle (Baltzan et al., 1962),

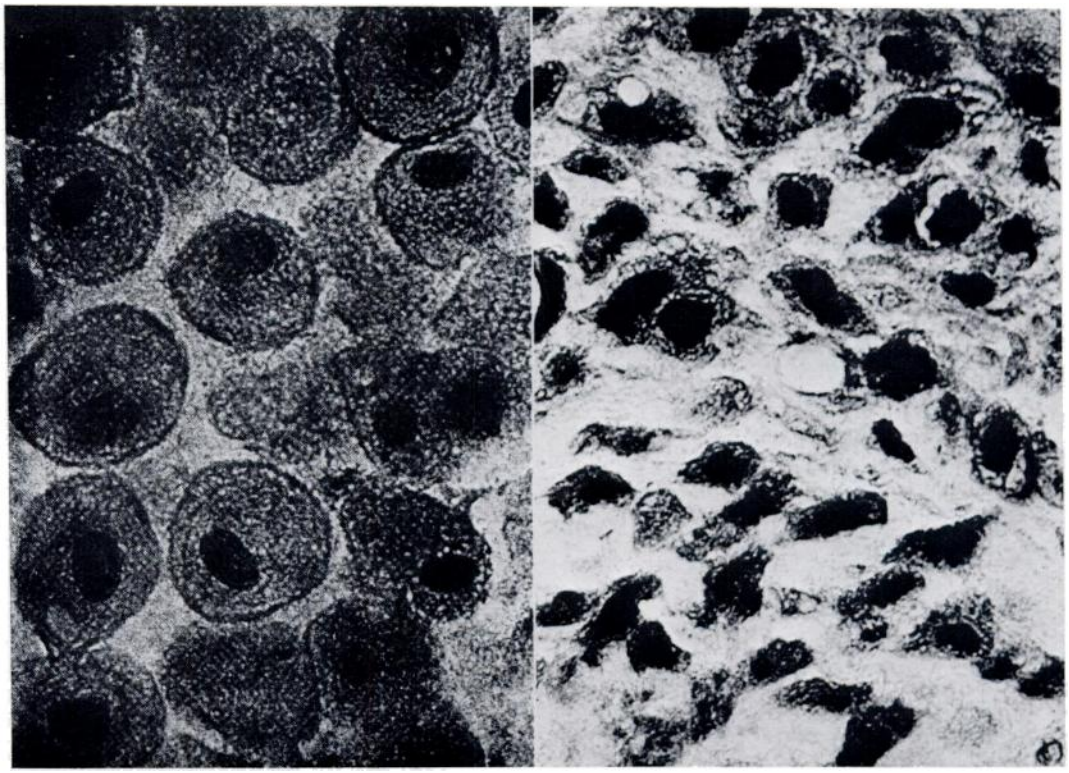

FIG. 8. Decidual cells stained with hematoxylin and eosin. On left, tissue from midpregnancy. On right, tissue from term pregnancy showing cellular degeneration. X910. (From Gustavii (1975) with permission of the Editor of the British Journal of Obstetrics and Gynaecology).

red blood cells (Jandl, 1965) and fetal brain (Adam et al., 1975). The activity of phospholipase A_2 in amnion is equal to that of decidua and greatly exceeds that of chorion and myometrium (Grieves and Liggins, 1976). Some of the amnion glycerophospholipids, especially phosphatidyl ethanolamine, are highly enriched in arachidonic acid (Robertson and Sprecher, 1968) and the turnover of arachidonic acid relative to palmitic acid in lecithin is rapid (Schwartz et al., 1976b). These characteristics of amnion suggest that it has a considerable potential for generation of arachidonic acid although it lacks the capacity to convert arachidonic acid to prostaglandins.

The properties of fetal membranes, deciduum and myometrium that are pertinent to prostaglandin synthesis are summarized in Table 3. When considered together, they suggest that the fetal membranes and deciduum may function as a unit, the membranes serving as a substantial source of arachidonic acid for prostaglandin synthesis in the deciduum and possibly the chorion.

The factors promoting selective incorporation of arachidonic into glycerophospholipids and, more importantly, the factors stimulating release of arachidonic acid are unknown. Gustavii (1975) suggested that progesterone stabilizes lysosomes thereby preventing release of phospholipase A_2. Schwarz et al. (1974) investigated progesterone binding in subcellular fractions of homogenates of chorioamnion and found evidence consistent with Gustavii's proposal. Labeled progesterone was found in highest concentration in lysosomal fractions and was not extractable with high concentrations of salt. Moreover, they found that the cytosol contains a progesterone-binding protein in low concentration in fetal membranes before 38 weeks of pregnancy but in much higher concentration at term. It differs from cytosol progesterone receptors and transcortin. This led Schwarz et al. (1974) to propose that a specific progesterone binding protein appears in the cytosol of the fetal membranes near term and competes with lysosomes for progesterone. As a consequence, the lysosomes become more un-

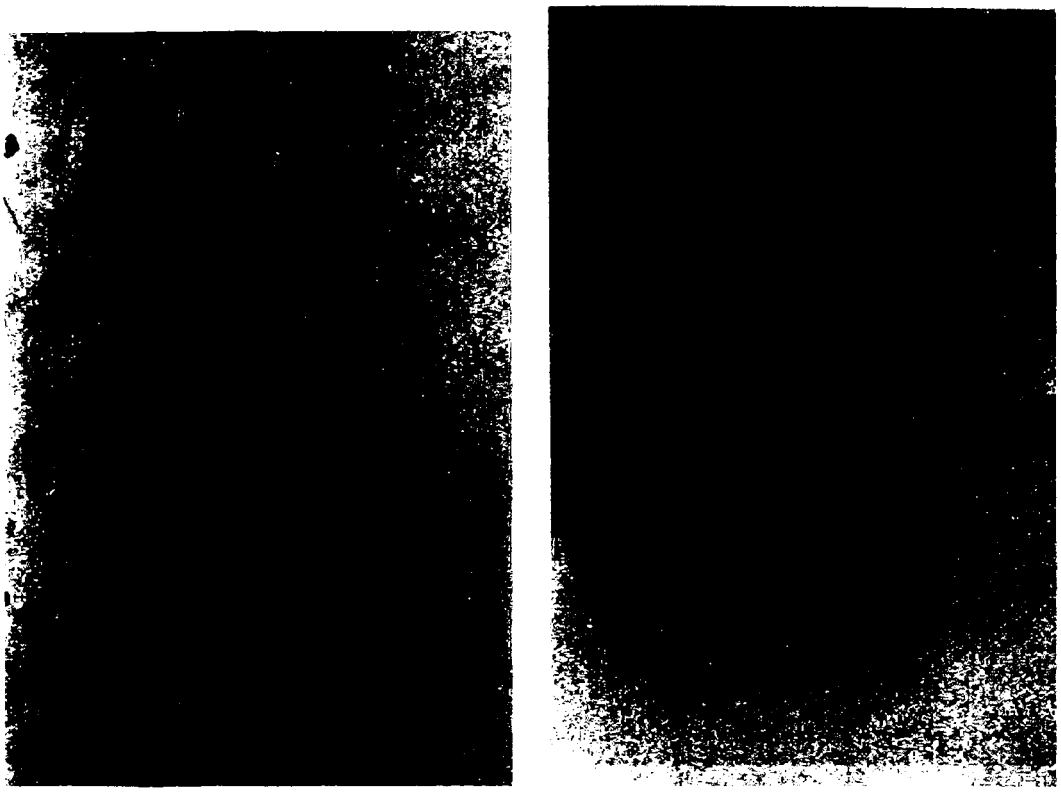

FIG. 9. Amniotic membrane obtained at caesarean section at term and stained with hematoxylin and eosin. On left, tissue fixed immediately. On right, tissue incubated at 37°C for 2 h in 0.9% sodium chloride solution before fixation. ×400.

stable and their contents leak out. Thus, in effect, there is a local withdrawal of progesterone in the membranes independent of maternal plasma levels. The cause for the rapid accumulation of progesterone binding protein is unknown.

TABLE 3. Comparison of factors related to prostaglandin production in uterine tissues.

	Amnion	Chorion	Deciduum	Myometrium
Tissue 'fragility'	++[a]	−[b]	+[c]	−[b]
Phospholipase activity	++[d]	±[d]	++[d]	±[d]
Enrichment of phospholipids with arachidonic acid	++[a,e]	++?[e]	++[e]	?
Prostaglandin synthesis	−[f]	+?[f]	+[g]	+[g]
Prostaglandin degradation	−[f]	++[f]	±[g]	±[g]

[a]Schwartz et al. (1976).

[b]Schwartz and Liggins, unpublished observations.

[c]Brunk and Gustavii (1973).

[d]Grieves and Liggins (1976).

[e]Schwarz et al. (1975).

[f]Keirse and Turnbull (1976).

[g]Sykes et al. (1975).

TWO MECHANISMS OF LABOR?

The forgoing discussion raises the question of whether there might, in any given species, be two mechanisms of labor—one in which the fetal adrenal is important and another which depends on an interaction between fetal membranes and deciduum. According to species, one or other system might be dominant. In some species such as sheep, the fetal role is dominant but in others such as nonhuman primates and humans, the latter system might be the more important. The local 'membrane mechanism' is seen as being a biological clock, able to determine a rather crude species-specific life span to pregnancy. Superimposed on the 'membrane mechanism' is a more refined system (the 'fetal adrenal mechanism') that adds greater accuracy to the timing of pregnancy duration. It should be added that yet another system (the 'maternal mechanism') may further refine the time of onset of labor. The three mechanisms might respectively determine the week, the day and the hours of birth.

It is possible that the membrane mechanism is merely a part of the fetal adrenal mechanism. On the other hand it might represent a maturational event, timed by the same sort of genetically-controlled clock that operates in maturing fetal organs. The rapid, precisely-timed appearance of an enzyme in, say, fetal liver is readily accepted as a normal part of maturation. Why not in fetal membranes? Maternal and fetal hormones might do no more than wind up the clock.

A local membrane mechanism that is not necessarily dependent on extraneous hormonal influences is consistent with findings in several species. Reference has been made already to human anencephalic pregnancy in which mean gestation length is approximately 40 weeks but the range is very wide. A similar observation was reported by Novy (1976) who hypophysectomized fetal rhesus monkey and found that a third were born prematurely, a third were born at term and the remaining third were born beyond term. A local mechanism is consistent also with widely spaced births of human twins in bicornuate uteri and with the observation that when premature labor is induced by fetal infusion of ACTH in sheep with twin lambs, the infused fetus invariably is born first (Liggins et al., 1976). Asymmetrical delivery was induced in rabbits by Costa and Csapo (1959) by dislocating one placenta in one horn of animals ovariectomized on Day 25; administration of oxytocin 9 h later caused delivery of all the fetuses in the horn containing the dislocated placenta whereas pregnancy was maintained in the other horn. Fetectomy experiments also are possibly relevant to this question. Dr. Lanman has described in his paper the results of his fetectomy experiments in rhesus monkeys. In the mouse, Newton (1935) fetectomized 20 animals in groups of five on Days 12, 13, 14 and 15 of pregnancy and observed parturition on Days 16-23. Twelve rats fetectomized between Days 9 and 13 delivered the placenta 8-12 days later (Selye et al., 1935). The consistent feature of these experiments is that pregnancy continues for some time after fetectomy. Delivery occurs very roughly at term but with a wide range compared to intact pregnancies.

Labor in human pregnancy may be initiated mainly by a genetically-controlled maturational signal arising in the fetal membrane and expressing itself through an interaction with the deciduum; fetal and maternal hormone may play a lesser, dispensible part.

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