HUMAN BIRTH

R.A. Greene

'When the child is grown big and the mother cannot continue to provide him with enough nourishment, he becomes agitated, breaks through the membranes, and incontinently passes out into the external world free from any bonds'
HIPPOCRATES, ON GENERATION, 4TH CENTURY BC

'The stimulus for labour may originate in certain states of vital development or physical expansion of the fundus, corpus or cervix uteri and in altered conditions of the fetus, liquor amnii or placenta and the loosening or decadence of the membranes....'
JAMES YOUNG SIMPSON, LECTURES ON MIDWIFERY, 1860

The safe and effective management of labour and delivery requires a clear understanding on the part of the birth attendant of the anatomy, physiology and biochemistry of human parturition and of its central participants – the mother and the infant. The 20th century, across most of which *Munro Kerr* has stretched, witnessed the most spectacular growth and advance of medical science and with it a steady improvement in our understanding of the birth process. A hundred years ago the obstetrician's art depended mainly on the insights brought by the giants of 18th century obstetrics, notably William Smellie (1697–1763) and William Hunter (1718–1783), both incidentally born within 20 miles of Munro Kerr's birthplace. Smellie, who became acknowledged as 'The Master of British Midwifery', was the consummate man-midwife and teacher. His monumental *Treatise on the Theory and Practice of Midwifery* (1752), based on his extensive clinical experience, described and defined the birth process as never before and formed the basis for the clinical conduct of labour. His definition of the mechanisms of labour shed light on the convoluted journey through the birth canal which the fetus is required to follow. His *Sett of Anatomical Tables with Explanations and an Abridgement of the Practice of Midwifery* (1754) amplified these fundamental principles. This atlas, for which Smellie employed the Dutch artist Jan van Rymsdyk, was only surpassed 20 years later when Hunter, employing the same artist, published his spectacular *Anatomy of the Human Gravid Uterus* (1774). When Munro Kerr was preparing the original *Operative Midwifery* in 1908 there had been little further progress. The relevant anatomy was fairly well understood but the physiology of the myometrium and cervix, and the biochemistry, endocrinology and pharmacology of human labour were almost entirely unknown. At this current time, the young obstetrician may consider that those mysteries have almost all been solved following a century of discoveries which saw the emergence of oxytocin, oestrogen, progesterone, prostaglandins and many other hitherto unknown substances. But it would be surprising indeed if the close of the 21st century does not reveal an even more complex picture.

CURRENT UNDERSTANDING

As a starting point for the wide range of clinical issues addressed within this textbook, a brief review follows of some of the key elements of basic medical science pertaining to human labour and delivery as currently understood. This, by necessity, will be superficial and selective. For more detailed and comprehensive accounts the reader should look to current textbooks of reproductive physiology, anatomy, biochemistry and endocrinology.

Labour may be regarded as a release from the inhibitory effects on the myometrium of various chemicals (progesterone, prostacyclin, relaxin, parathyroid hormone-related peptide, nitric oxide, calcitonin gene-related peptide and others) active during pregnancy, rather than as an active process secondary to myometrial stimulation.

Myometrial Function

The myometrium is the engine which drives human labour, during which it displays a highly sophisticated and co-ordinated set of forces. The simple objective of these is to efface and dilate the cervix and push the fetus through the birth canal. In contrast to other smooth muscle systems, the myometrium displays three unique properties which are crucial for its function:

1. It must remain quiescent for the greater part of human pregnancy, suppressing its natural instinct to contract until called upon to do so at the appointed time.
2. During labour it must display a pattern which affords adequate periods of relaxation between contractions without which placental blood flow and fetal oxygenation would be compromised.
3. It possesses the capacity for *retraction*, vital to prevent exsanguination after delivery but also essential during labour. Retraction is a unique property of uterine muscle whereby a shorter length of the muscle fibre is maintained, without the consumption of energy, even after the contraction that produced the decrease in length has passed. As the cervix is

effaced and pulled around the fetal presenting part, an inability of the myometrial fibres in the uterine corpus to retract, in essence to steadily reduce their relaxed lengths, would mean that the tension on the cervix could not be maintained.

At its most basic, human labour may be regarded as an interaction between the corpus and the cervix (Fig. 1.1). For the maintenance of pregnancy the corpus must be quiescent and the cervix closed and uneffaced. In labour the corpus contracts and the cervix yields. A useful analogy may be to compare this process to the experience of putting on, for the first time, a roll-neck pullover. Just as with the fetus, the head must be flexed to present its smallest diameters to the cervix, or neck of the pullover, which is effaced round the presenting part and ultimately dilated as a result of traction applied by the arms, which are in this connection analogous to the myometrial fibres. Although it has been conventional to acknowledge a 'lower uterine segment' arising from the uterine isthmus (between the non-pregnant corpus and cervix), in practice it may be more helpful simply to see the boundary between corpus and cervix as the 'fibromuscular junction'
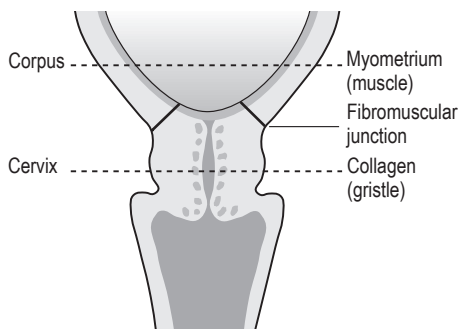

FIG. 1.1 ■ Diagrammatic representation of the relationship of the uterine corpus and cervix in mid pregnancy.

which marks the change from a mostly muscular corpus to a predominantly fibrous cervix. Obstetric purists may argue that the concept of a 'lower segment' is helpful in the definition of placenta praevia and in directing the site of contemporary caesarean sections but, those issues apart, it is of little relevance and it is a difficult concept to define either anatomically or physiologically. At its simplest, contraction of the myometrial cell requires actin and myosin to combine in the contractile filament actinomyosin (Fig. 1.2). This reaction is catalysed by the enzyme myosin light-chain kinase, which is heavily calcium dependent. Calcium in turn relies for its availability on oxytocin and prostaglandin $F_{2\alpha}$, which assist its transport into the cell and also free it from intracellular stores (sarcoplasmic reticulum).

As term approaches, the uterus becomes activated in response to stimulants e.g. oestrogen. There is an increased expression of contraction-associated proteins and myometrial receptors for prostaglandins and oxytocin. A particular insight into how the myometrial effort is co-ordinated into a concerted function came from the recognition of the essential requirement for gap junctions (biochemically characterized as connexin-43) to be formed between individual myometrial cells, allowing cell-to-cell transmission of electrical impulses and ions. Thus, the corpus can display a wave of contractility propagated across its cell population which becomes a functional syncytium rather than a disorganized mass of individual muscle fibres.

Following activation, the uterus can be stimulated to contract by the action of uterotonic agents such as prostaglandin E_2, $F_{2\alpha}$ and oxytocin.

The Cervix

The recognition, little more than 50 years ago, that the cervix possesses a distinct structure based on collagen-rich
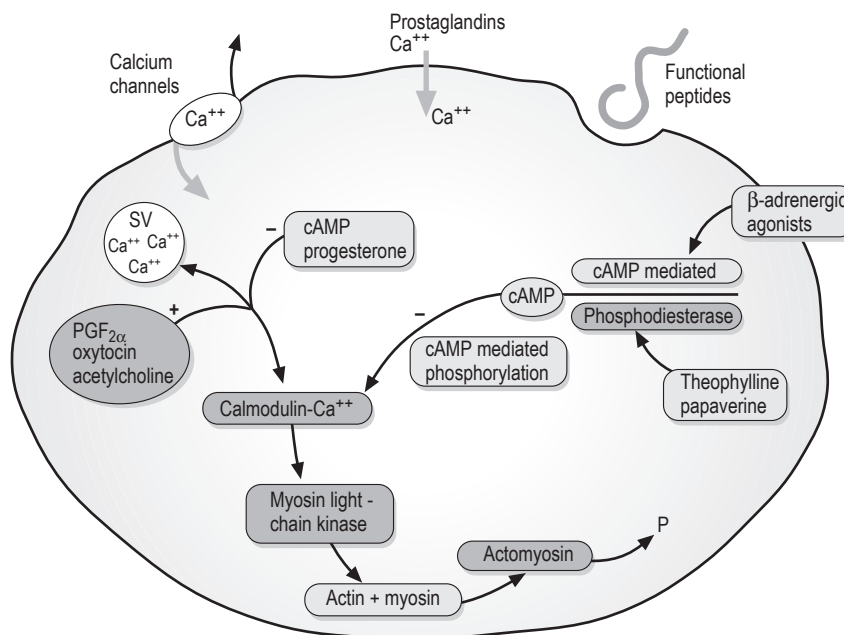

FIG. 1.2 ■ Schematic representation of the contractile process of the myometrial cell. Those components shown in dark boxes represent contraction, those in light boxes represent relaxation.

FIG. 1.3 ■ Original dissections prepared by William Hunter in the 18th century. That on the left (a) shows the lower part of the uterus, cervix, vagina, bladder and urethra in sagittal section in the last few weeks of pregnancy. That on the right (b) shows the cervix from the intrauterine aspect as it undergoes effacement in the last month of pregnancy (the fibromuscular junction is now at the periphery of this specimen).

connective tissue rather than smooth muscle has been fundamental to a better understanding of its function. It is thus not a 'sphincter' of the uterus but rather a rigid obstacle to delivery which has to undergo a profound change in consistency to permit effacement, dilatation, and delivery to take place (Fig. 1.3). That change is the process we now describe as 'cervical ripening'.

The requisite loosening and degradation of the collagen bundles is now recognized as having much in common with an inflammatory process, which requires the participation of inflammatory mediators including prostaglandin E_2 and cytokines (especially interleukin (IL)-8), the recruitment of neutrophils and the synthesis of matrix metalloproteinases, including collagenases and elastase (Fig. 1.4).

BIOLOGICAL CONTROL OF LABOUR – TRIGGERING AND MAINTENANCE

The process by which the labour is triggered and maintained has been the subject of intensive investigations. The clinical drive to this area of research has been the desire:

- to better understand, prevent or suppress preterm labour with all its complications
- to improve our ability to correct abnormal uterine action and poor progress in labour
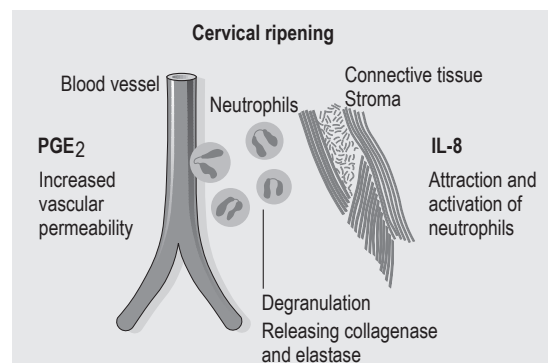- to enhance our capacity to induce effective labour when indicated by clinical circumstances.

FIG. 1.4 ■ Schematic representation of the control of cervical ripening. The collagen of the cervical stroma is broken down by matrix metalloproteinases, such as collagenase and elastase derived from neutrophils in an inflammatory-like process which requires them to be drawn into the tissue under the influence of interleukin-8 (IL-8) from capillaries which have been dilated and made more permeable by prostaglandin E_2 (PGE_2).

The following brief review oversimplifies what is a most complex set of interactions, but it may suffice as a basis for rational clinical intervention.

It is likely that a biochemical cascade exists (as in many processes in the body, e.g. thrombus formation) at term which decreases the factors maintaining uterine quiescence and/or enhances factors promoting uterine activity (Smith, 2007). Given its importance (the birth of the next generation), such a cascade as others will likely have multiple redundant loops to ensure a fail-safe system. In such systems, each element is connected to the next in a sequential

fashion, and many of the elements demonstrate positive feed-forward characteristics. This makes it unlikely a single mechanism is responsible for the initiation of labour. Therefore, it is prudent to describe such a 'cascade' as being responsible for 'promoting', rather than 'initiating', labour.

Current hypotheses suggest a dynamic biochemical dialogue between the fetus and mother (paracrine/autocrine events) with a probable genetic regulation of the molecular events that occur before and during labour.

It is now recognized that the trigger for parturition likely comes from the fetus rather than from the mother. The maturing fetal brain is thought to provoke the release of corticotrophin from the fetal pituitary gland (Fig. 1.5) and oxytocin. This may be considered analogous to the switching on of pituitary gonadotrophin production at the time of puberty. The fetal adrenal gland responds by releasing two main products, cortisol and dehydroepiandrosterone sulphate:

- Cortisol stimulates fetal pulmonary surfactant production to mature the lungs for extrauterine function and may also influence other organ systems. This is thought to result in changes in the composition of the amniotic fluid which provoke the release of prostaglandin E_2 from the amnion. This may be important for a direct influence on the cervix, especially focused at the internal os as this is the portion of the cervix which lies in intimate contact with the fetal membranes. The internal os needs to ripen first to initiate cervical effacement. To do this the activity of the principal prostaglandin degrading enzyme prostaglandin dehydrogenase within the chorion must decline, a phenomenon which has
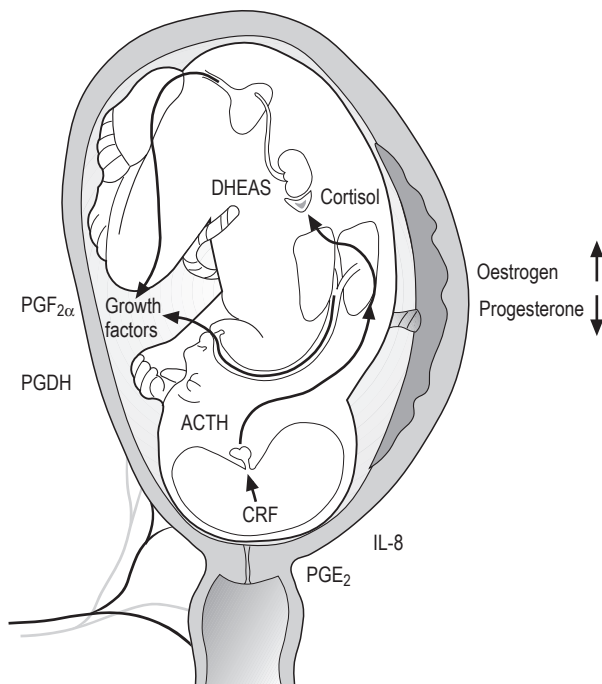
recently been confirmed.
- Dehydroepiandrosterone sulphate is metabolized in the placenta to enhance oestrogen levels which stimulates the myometrium as outlined earlier. Oestrogen may provoke the release of prostaglandin $F_{2\alpha}$ from its richest source, the decidua, thereby exciting myometrial contractions.
- The fetal pituitary secretes oxytocin into the maternal circulation, with calculated oxytocin secretion rates from the fetus of a baseline of 1 mU/min prior to labour and approximately 3 mU/min after spontaneous labour. Maternal serum oxytocin levels are not increased prior to the onset of labour or during the first stage of labour; therefore, oxytocin derived from the fetus (and local decidua/other uterine sources) could act on myometrial oxytocin receptors in a paracrine fashion to initiate and maintain effective uterine contractions.

Inflammation and Labour

Cytokines have long been implicated in the pathophysiology of preterm labour associated with intra-amniotic infection. They are also involved in normal term labour. Proinflammatory mediator levels - IL-6 and tumour necrosis factor alpha (TNF-α) - increase in the maternal peripheral circulation before the onset of spontaneous term labour. The fetus may produce physical (distension) and hormonal signals that stimulate macrophage migration to the uterus with the release of cytokines and the activation of an inflammatory process.

Concentrations of IL-8 in human myometrium, decidua and fetal membranes are increased during labour. IL-8 is a potent chemotactic for neutrophils. It may cause an increase in collagenase enzyme activity leading to cervical ripening and/or spontaneous rupture of membranes. Cytokines and prostaglandin production appear to interact and to accelerate each other's production. It has also been proposed that the increased inflammatory response promotes uterine contractility via direct activation of contractile genes (e.g. COX-2, oxytocin receptor, connexin) and/or impairment of the capacity of progesterone to mediate uterine quiescence (Parry et al, 1998).

MEMBRANE RUPTURE

The strength and integrity of fetal membranes derive from extracellular membrane proteins including collagens, fibronectin and laminins. Matrix metalloproteases (MMPs) are a family of enzymes with varied substrate specificities that decrease membrane strength by increasing collagen degradation. Tissue inhibitors of MMPs (TIMPs) bind to MMPs and shut down proteolysis, thereby helping to maintain membrane integrity. The fetal membranes normally remain intact until term due to low MMP activity and high levels of TIMPs. Peripartum activation of MMPs at term may trigger a cascade of events that reduce fetal membrane integrity and promote rupture of membrane. Stretch and shear forces from uterine contractions during labour probably contribute to membrane rupture, as well.

FIG. 1.5 ■ Fetal control of the onset of labour is thought to result from activation of its hypothalamic–pituitary–adrenal axis, which leads in turn to modification of placental steroid production and activation of prostaglandins in the decidua and cervix. *ACTH,* Adrenocorticotrophic hormone; *CRF,* corticotrophin-releasing factor; *DHEAS,* dehydroepiandrosterone sulphate; *IL,* interleukin; *PG,* prostaglandin; *PGDH,* prostaglandin dehydrogenase.

The precise aetiology of peripartum MMP activation is not known; several factors may play a role in this process; such as TNF-α, IL-1, prostaglandins E$_2$ and F$_{2\alpha}$ appear to increase collagenase activity and activate inflammatory pathways in fetal membranes at parturition (Maymon et al, 2011). Mechanical stretching of fetal membranes activates MMP-1 and MMP-3 and induces IL-8 expression in amnion and chorion cells (Nemeth et al, 2000).

Progesterone remains an enigma. It is known to inhibit both myometrial contractility and the formation of gap junctions, and is also recognized as supporting the activity of prostaglandin dehydrogenase, but evidence for its withdrawal prior to parturition remains elusive. It seems likely that there is either a process whereby its activity at tissue level declines without a drop in circulating levels, or simply that its influence is overcome by other factors. We can therefore postulate that a cascade of endocrine

changes initiated by the fetal brain – hypothalamic–pituitary–adrenal axis - results in the activation of a variety of endocrine and inflammatory substances which have the effect of co-ordinating key events:

- maturing essential fetal organ systems, notably the lungs, for the challenges of extra-uterine life
- initiating changes in the myometrium to enhance its capacity to contract effectively
- transforming the rigid cervix into a compliant and readily dilatable structure
- stimulating the myometrial contractions which will ultimately deliver the fetus through the birth canal
- promoting the inflammatory process before and during labour to allow cervical change, membrane rupture and facilitate myometrial contractions.

Fig 1.6 summarizes the key biochemical components which are thought to control the inflammatory-type processes which convert the stroma of the cervix from a rigid structure to a soft and compliant one, and the activation of the myometrial contractility which ultimately brings about its effacement and dilatation.

This brief overview is of necessity simplified. The control of the birth process requires the participation of a myriad of other factors, such as adhesion molecules and receptors for hormones and prostaglandins, as well as other hormones such as vasopressin and relaxin. Perhaps the most important recent change in thinking has been to see the whole process of parturition as an inflammatory-type event. This has vital consequences for our understanding of those pregnancies which do not follow the normal pattern of labour onset and progress, either because it is delayed or activated prematurely. The role of infection in the latter is gaining increasing importance and it seems likely that some women may be at increased risk of preterm labour on account of an increased susceptibility to infection from a deficiency of endogenous antimicrobial substances (Fig. 1.7).
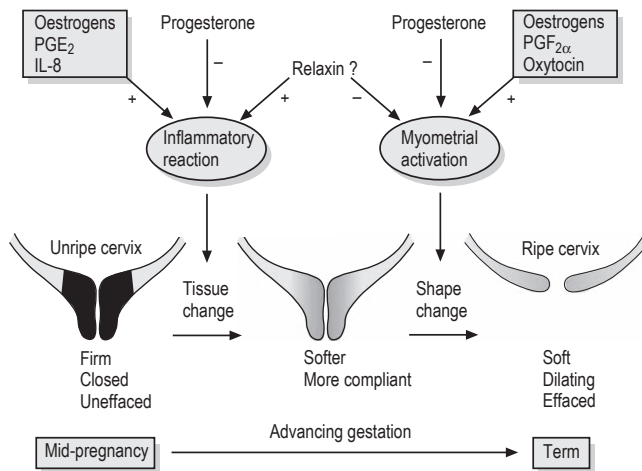

FIG. 1.6 ■ A schematic representation of the factors which bring about the softening and dilation of the cervix during the transition from pregnancy maintenance to parturition. *IL*, Interleukin; *PG,* prostaglandin.
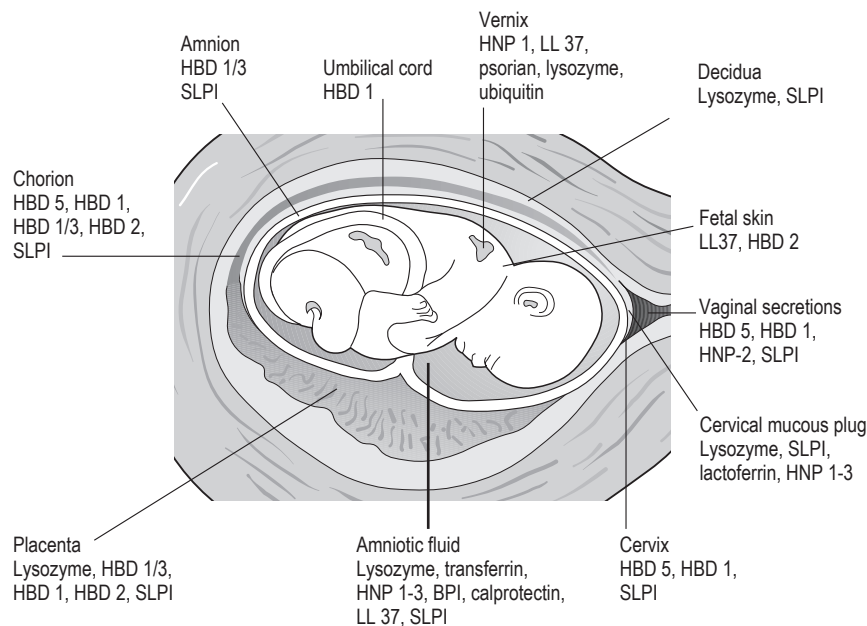

FIG. 1.7 ■ Some of the natural antimicrobial substances which may be important in resisting infection during pregnancy. A deficiency of these may predispose to preterm delivery. (By permission of Dr Sarah Stock.) *HBD,* Human Beta Defensin; *HNP,* Human Neutrophil Defensin; *SLPI,* secretory leukocyte peptidase inhibitor; *LL 37,* the only cathelicidin-derived antimicrobial peptide found in humans.

A better understanding of the pathway to normal birth should provide the basis for identifying points along the pathway at which a pathological process may precipitate preterm birth. The effects of stress may be mediated by increased cortisol levels in the maternal or fetal compartments and consequent increases in placental corticotrophin-releasing hormone expression. Infection activates inflammation and may stimulate prostaglandin synthesis in fetal membranes. Abruption appears to affect the myometrium directly through the release of thrombin, a potent stimulator of myometrial contraction. In the case of multiple gestation and polyhydramnios, increased uterine stretching activates myometrial contractility. Such understanding may also assist improved intervention outcomes, perhaps through better selection of appropriate cases for induction of labour.

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